

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Drug Use Review

Date: September 15, 2017

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Subject: Utilization Trends for Pregabalin and Gabapentin

Drug Name(s): Lyrica® CR (Pregabalin)

Application Type/Number: NDA 209501

Applicant/sponsor: Pfizer Inc.

OSE RCM #: 2017-619

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EXECUTIVE SUMMARY

1 INTRODUCTION

The Control Substance Staff (CSS) in the Office of the Center Director requested the Division of Epidemiology II (DEPI II) to provide relevant epidemiological data for the use and abuse of pregabalin with other drugs, specifically with opioid analgesics, due to risk of potential adverse respiratory reactions. This consult was generated in response to an extended-release (ER) pregabalin product currently under review for approval. Drug utilization patterns were assessed in order to capture the use of both, pregabalin and gabapentin, and to provide informational context for the epidemiological studies. This review summarizes the drug utilization of pregabalin and gabapentin as a comparator, from 2012 through 2016 in the U.S. outpatient retail pharmacies.

Outpatient retail pharmacy utilization data analyses show that approximately (b) (4) patients received a dispensed prescription for pregabalin in 2016. The majority of pregabalin utilization was observed in adult patients 18-64 years in the outpatient retail setting. Based on office-based physician survey data, pregabalin was reported to be used with opioid analgesics for approximately 19% of total drug occurrences mentioned during an office visit. In terms of indications for use, drug use mentions of gabapentin and pregabalin products based on the survey data were primarily associated with the diseases of the musculoskeletal system and connective tissue such as back pain.

The results described in this review consist of prescription and patient counts as denominator data. These results will be combined with poison control center data, from the American Association of Poison Control Centers (AAPCC) and incorporated into a separate comprehensive review.

1.1 BACKGROUNDⁱ

Pregabalin (a gabapentinoid) is an anticonvulsant that is indicated for the following conditions below:

- Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- Post herpetic neuralgia (PHN)
- Adjunctive therapy for adult patients with partial onset seizures
- Fibromyalgia
- Neuropathic pain associated with spinal cord injury

Product information for the pregabalin products are provided in the table below. For comparison, another gabapentinoid; gabapentin, was included in this analysis because the compound is similar to pregabalin structurally and may exhibit similar adverse events when used concomitantly with opioids.

1.2 PRODUCT INFORMATIONⁱⁱ

Approval Status	Trade Name (Generic)	Application Number	Applicant	Strengths	Dosage Form/Route
Under Review for Approval	Lyrica CR (Pregabalin ER)	NDA 209501	Pfizer Inc.	82.5, 165, 330-mg	Tablet Extended-Release/Oral
December 30, 2004	Lyrica (Pregabalin)	NDA 021446	PF Prism CV	25, 50, 75, 100, 150, 200, 225, 300-mg	Capsule/Oral
January 4, 2010	Lyrica (Pregabalin)	NDA 022488	PF Prism CV	20 mg/mL	Solution/Oral
December 30, 2004	Lyrica (Pregabalin)	NDA 021723	CP Pharms	25, 50, 75, 100, 150, 200, 225, 300-mg	Capsule/Oral
June 10, 2005	Lyrica (Pregabalin)	NDA 021724	CP Pharms	25, 50, 75, 100, 150, 200, 225, 300-mg	Capsule/Oral

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed description and limitation of the databases are included in Appendix 2.

2.1 DATA SOURCES USED

The QuintilesIMS, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for pregabalin and gabapentin from U.S. outpatient retail pharmacies, from 2012 through 2016, annually.

The QuintilesIMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for pregabalin and gabapentin from U.S. outpatient retail pharmacies, stratified by patient age (0-17, 18-64, 65 years and older), from 2012 through 2016, annually.

inVentiv Health Research & Insights, LLC., Treatment Answers™ with Pain Panel, a U.S. office-based physician survey database was used to obtain top groups of diagnoses associated with the use of pregabalin and gabapentin in 2016. Diagnoses data by number of drug use mentions¹ were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence were applied to the estimates. The database was also used to provide information on the occurrences of pregabalin and gabapentin, used alone or concomitantly, with other drugs in 2016.

3 RESULTS

3.1 SETTINGS OF CARE

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to determine the various settings of care where pregabalin and gabapentin were distributed by the manufacturer in 2016. Sales data by the number of bottles/packages sold from manufacturer to all U.S. channels of distribution showed that approximately 80% of pregabalin was primarily distributed to outpatient retail pharmacies, 11% to non-retail pharmacies, and 9% to mail-order/specialty pharmacies. Similarly, approximately 70% of gabapentin was primarily distributed to outpatient retail pharmacies, 21% to non-retail pharmacies, and 9% to mail-order/specialty pharmacies.ⁱⁱⁱ Only outpatient retail pharmacy utilization patterns were examined for pregabalin and gabapentin. Mail-order/specialty pharmacy and non-retail pharmacy settings data (i.e., hospitals, clinics) were not included in this review.

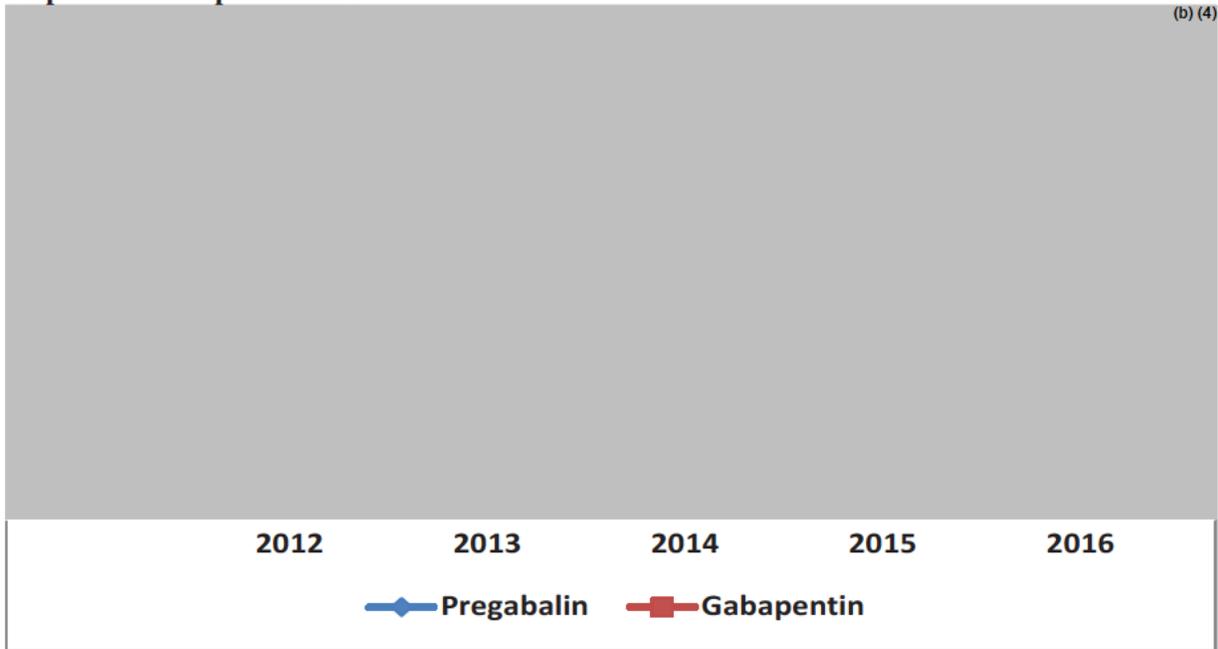
3.2 PRESCRIPTION DATA

Figure 3.2.1 below and Table 3.2.1 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for pregabalin and gabapentin from U.S. outpatient retail pharmacies from 2012 through 2016, annually. The total number of prescriptions dispensed for pregabalin increased by (b) (4)% from approximately (b) (4) in 2012 to approximately (b) (4) in 2016. In comparison, the number of prescriptions dispensed for gabapentin increased by (b) (4)% from approximately (b) (4) in 2012 to (b) (4) in 2016.

¹ A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Figure 3.2.1

Nationally estimated number of dispensed prescriptions for pregabalin and gabapentin^a from U.S. outpatient retail pharmacies



Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted May 2017.

^a Gabapentin include gabapentin encarbriil (gabapentin prodrug)

3.3 PATIENT DATA

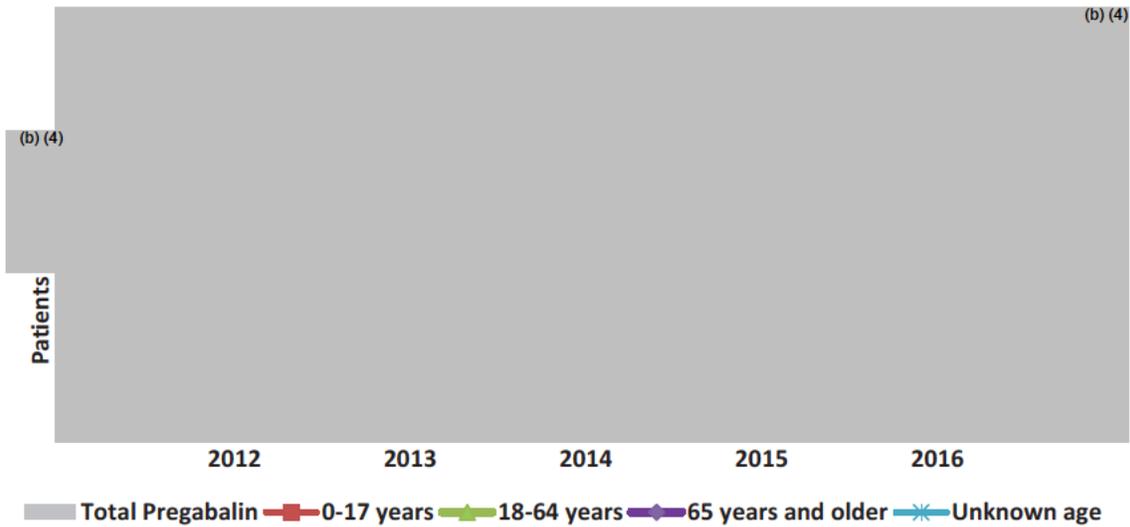
Figures 3.3.1 and 3.3.2 below and Table 3.3.1 in Appendix 1 provide the nationally estimated number of patients who received a prescription for pregabalin and gabapentin, stratified by patient age (0-17, 18-64, 65 years and older) from U.S. outpatient retail pharmacies from 2012 through 2016, annually.

Similar to prescription trends, patient utilization for both drugs increased in the examined time period. The number of patients who received a dispensed prescription for pregabalin increase by (b) (4)% from approximately (b) (4) patients in 2012 to approximately (b) (4) patients in 2016. The number of patients who received a dispensed prescription for gabapentin increased by (b) (4)% from approximately (b) (4) patients in 2012 to approximately (b) (4) patients in 2016.

The largest proportion of patients who received a dispensed prescription for pregabalin and gabapentin were patients aged 18-64 years, accounting for approximately (b) (4)% of the total, followed by patients aged 65 years and older at approximately (b) (4)% throughout the entire study period. Pediatric patients aged 0-17 years accounted for less than (b) (4)% of total patients for pregabalin and (b) (4)% for gabapentin.

Figure 3.3.1

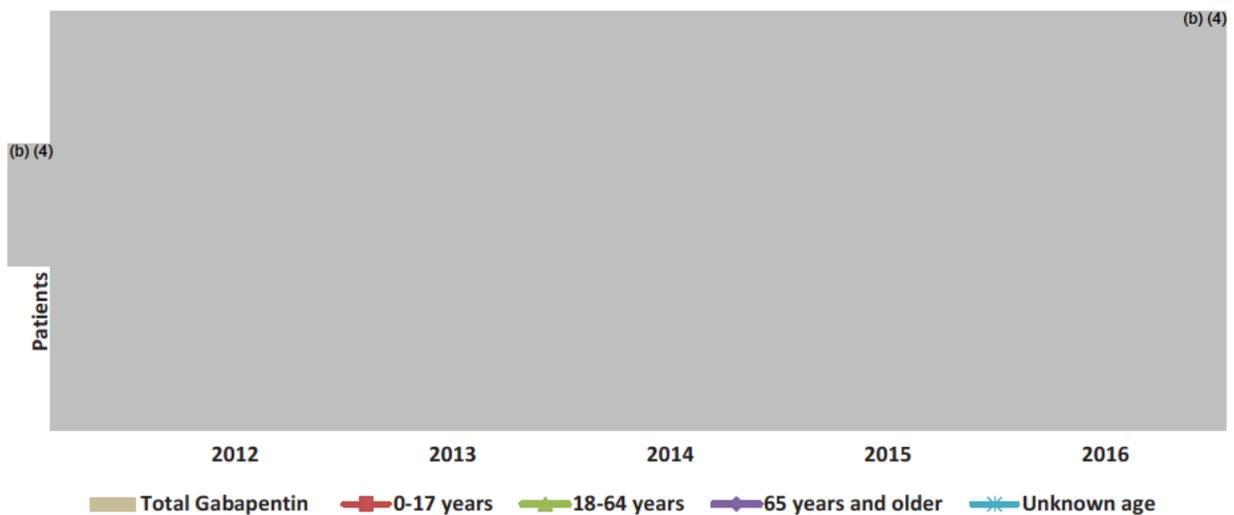
Nationally estimated number of patients* who received a dispensed prescription for pregabalin, stratified by age, from U.S. outpatient retail pharmacies



Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted May 2017.
*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

Figure 3.3.2

Nationally estimated number of patients* who received a dispensed prescription for gabapentin, stratified by age, from U.S. outpatient retail pharmacies, 2012-2016



Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted May 2017.
^a Gabapentin include gabapentin encarbriil (gabapentin prodrug)
*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

3.4 DIAGNOSIS DATA

Table 3.4.1 in Appendix 1 provides data on groups of diagnoses (ICD-10 codes) in terms of drug use mentions associated with the utilization of pregabalin and gabapentin products as reported by U.S. office-based physician surveys. In 2016, the total gabapentinoid market accounted for approximately (b) (4) drug use mentions. Of the total, gabapentin accounted for (b) (4)% of the drug use mentions while pregabalin accounted for approximately (b) (4)% of the drug use mentions.

For gabapentin and pregabalin, diagnoses associated with “diseases of the musculoskeletal system and connective tissue” accounted for the majority of drug use mentions at approximately (b) (4)% and (b) (4)%, respectively; of which the majority of mentions were for dorsalgia or unspecified soft tissue pain disorders. Diagnoses related to “diseases of the nervous system” followed at (b) (4)% for gabapentin and (b) (4)% of total drug use mentions for pregabalin. Of the diagnoses related to “diseases of the nervous system” for gabapentin, nerve pain accounted for the majority of drug use mentions; a small proportion were for diagnoses related to seizure disorders (data not shown).

3.5 CONCOMITANT DATA

Table 3.5.1 below provides the estimated number of drug occurrences² associated with pregabalin, either used alone or with another drug, as reported by U.S. office-based physician survey database for 2016.

A total of (b) (4) drug occurrences for pregabalin were captured in 2016. Of the total, the majority reported pregabalin as being “used alone” accounting for (b) (4)% of the drug occurrences. Approximately (b) (4)% of drug occurrences reported pregabalin to be used along with “oxycodone”. Approximately (b) (4)% of drug occurrences reported pregabalin to be used along with “hydrocodone-acetaminophen” or “oxycodone-acetaminophen”.

Using these data, in 2016 pregabalin was reported with the use of opioid analgesics in approximately 19% of drug occurrences for pregabalin. When 2016 data were compared to data from 2012, very little change was observed in the proportion of pregabalin reported with opioid analgesics (data from 2012 are not shown in this review).

² The term “drug occurrences” to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a “drug occurrence” does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

Table 3.5.1

Top 10 drug occurrences for pregabalin, used alone or with another drug, reported from U.S.

(b) (4)

Source: InVentiv Health Research & Insights, LLC, TreatmentAnswers™ Audit. Year 2016. Data extracted May 2017.

Note: inVentiv Health Research & Insights, LLC, Treatment Answers™ cautions that data below 100,000 projected mentions or occurrences may not represent national level trends because results below this threshold represent insufficient raw physician responses prior to applied projection factors.

Table 3.5.2 below provides the estimated number of drug occurrences associated with gabapentin, either used alone or with another drug, as reported by U.S. office-based physician survey database for 2016.

A total of (b) (4) drug occurrences for gabapentin were captured in 2016. Of the total, the majority reported gabapentin as being “used alone” accounting for (b) (4)% of the drug occurrences. Approximately (b) (4)% of drug occurrences reported gabapentin to be used along with “hydrocodone-acetaminophen”.

Approximately (b) (4)% of drug occurrences reported gabapentin to be used along with “cyclobenzaprine” or “oxycodone”.

Using these data, in 2016 gabapentin was reported with the use of opioid analgesics in approximately (b) (4)% of drug occurrences for gabapentin. When 2016 data were compared to data from 2012, very little change was observed in the proportion of gabapentin reported with opioid analgesics (data from 2012 are not shown in this review).

Table 3.5.2

Top 10 drug occurrences for gabapentin, used alone or with another drug, reported from U.S. office-based physician survey data in 2016

(b) (4)



Source: InVentiv Health Research & Insights, LLC, TreatmentAnswers™ Audit. Year 2016. Data extracted July 2017.

Note: inVentiv Health Research & Insights, LLC, Treatment Answers™ cautions that data below 100,000 projected mentions or occurrences may not represent national level trends because results below this threshold represent insufficient raw physician responses prior to applied projection factors.

4 DISCUSSION

This review provides drug utilization data for gabapentinoids (pregabalin and gabapentin), in the U.S. outpatient retail setting. Increasing utilization trends were seen in both the patient and prescription data for pregabalin and gabapentin products. During the examined time period, approximately (b) (4) patients received a dispensed prescription for pregabalin annually. Of the total, adult patients aged 18-64 years accounted for the largest proportion, followed by elderly patients aged 65 years and older. In comparison, the utilization of gabapentin was five to six times higher than pregabalin. Possible reasons for higher utilization of gabapentin over pregabalin may be attributed to multiple factors such as 1) gabapentin is not scheduled as a controlled substance so more accessible to patients compared to pregabalin (Schedule V), 2) indicated for use in pediatric patients for adjunct therapy in treatment of epilepsy with partial onset seizures, and 3) gabapentin has several off-label uses such as alcohol withdrawal, fibromyalgia and restless legs syndrome, and 4) gabapentin has a longer marketing history and is available in less expensive generic formulations^{iv}. However, our study did not assess the reasons behind the trends in utilization.

According to the office-based physician survey data in 2016, reported drug use mentions of gabapentin and pregabalin products were primarily associated with the diseases of the musculoskeletal system and connective tissue, such as back pain and unspecified soft tissue pain. Of note, based on the survey data, use of gabapentin for diagnoses related to seizure disorders was low. In addition, the office-based physician survey data were used to characterize the concomitant use of pregabalin or gabapentin with other drugs. The term "drug occurrences" refers to the number of times a product has been reported on a survey during an office-based patient visit and may not result in a dispensed prescription; rather it represents the prescriber's intention to treat. Therefore, these results do not represent a patient-level claims-based analysis of concurrent use between opioid analgesics and pregabalin or gabapentin but do

show possible concomitant use where the prescriber is aware of the use of two or more products together. The data presented based on surveys are likely an underestimation of the total concurrent use of these drugs as data on opioid analgesic prescriptions written by a different prescriber or during different visit by the same prescriber may not be reported. In addition, the “drug exposure” estimates may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed. However, these data indicate that concomitant use of pregabalin or gabapentin with opioids and other CNS depressants prescribed by the same prescriber does occur.

Outpatient utilization trends were examined for this review, the findings provided may not apply to other settings of care in which these products are also used such as non-federal hospitals, clinics, or mail-order pharmacies. However, the outpatient setting accounted for the majority of pregabalin and gabapentin use based on sales distribution data and is likely more relevant for an analysis of the risk of abuse and misuse as there is less oversight by a healthcare provider in comparison to other settings of care such as the inpatient setting.

5 CONCLUSIONS

Outpatient retail pharmacy utilization data analyses show that approximately (b) (4) patients received a dispensed prescription for pregabalin in 2016. The majority of pregabalin utilization was observed in adult patients 18-64 years in the outpatient retail setting. Based on office-based physician survey data, reported drug use mentions of gabapentin and pregabalin products were primarily associated with the diseases of the musculoskeletal system and connective tissue such as back pain and other soft tissue pain. In addition, gabapentin and pregabalin was reported to be used with opioid analgesics for approximately and (b) (4) % of drug occurrences, respectively.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 3.2.1

Nationally estimated number of dispensed prescriptions for pregabalin and gabapentin^a from U.S. outpatient retail pharmacies, from 2012-2016, annually

(b) (4)

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted May 2017.

^a Gabapentin include gabapentin encarbriil (gabapentin prodrug)

Figure 3.3.1

Nationally estimated number of patients* who received a dispensed prescription for pregabalin and gabapentin^a, stratified by age, from U.S. outpatient retail pharmacies

(b) (4)

Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted May 2017.

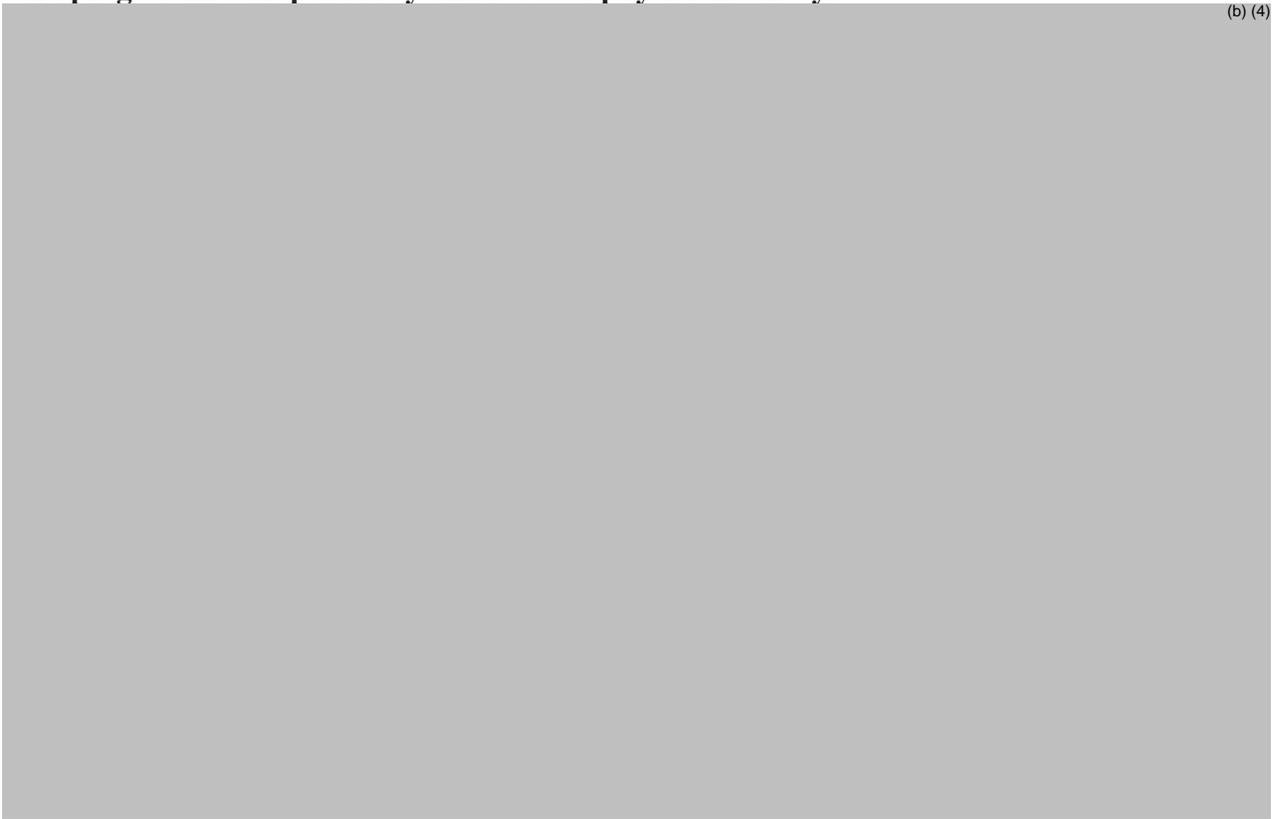
^a Gabapentin include gabapentin encarbriil (gabapentin prodrug)

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

Table 3.4.1

Diagnoses (ICD-10) in terms of drug use mentions* associated with the use of gabapentin and pregabalin as reported by office-based physician surveys

(b) (4)



Source: inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel. Year 2016. Data extracted Aug 2017.

*inVentiv Health Research and Insights LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over (b) (4) prescription claims per year, captured from a sample of the universe of approximately (b) (4) pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly (b) (4)% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately (b) (4)% (varies by class and geography) of mail service pharmacies and approximately (b) (4)% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over (b) (4) prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to

pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

6.3 REFERENCES

ⁱ U.S. Food and Drug Administration: Drugs@FDA. Lyrica CR Label Information. Accessed May 2017. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

ⁱⁱ U.S. Food and Drug Administration: Drugs@FDA. Accessed May 2017. Available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

ⁱⁱⁱ QuintilesIMS, IMS National Sales Perspectives™. Year 2016. Extracted May 2017.

^{iv} Gabapentin: Drug Information. UpToDate®. Lexi-Comp. Wolters Kluwer Health, Inc. Available at: <https://www.uptodate.com/>. Accessed July 10, 2017.

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/s/

JENNIE Z WONG
09/15/2017

RAJDEEP K GILL
09/15/2017

GRACE CHAI
09/15/2017

Consultative Review on NDA 209501

Drug: Lyrica CR (Pregabalin Extended Release)

Indication: Management of Neuropathic Pain associated with Diabetic Peripheral Neuropathy

Management of Postherpetic Neuralgia

Management of Fibromyalgia

Consult Date: January 10, 2017

Date Received / Division: January 10, 2017

Date Review Completed: September 7, 2017

Reviewer: Philip H. Sheridan, MD

Background:

This consultation to the Division of Neurology Products (DNP) from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) concerns the new NDA submitted by Pfizer for Lyrica CR (Pregabalin Extended Release) on December 15, 2016.

The proposed indications in the NDA are for the Management of Neuropathic Pain associated with Diabetic Peripheral Neuropathy, Management of Postherpetic Neuralgia, and Management of Fibromyalgia.

DAAAP asked for DNP comments and recommendations concerning the sponsor's proposed labeling language with regard to Study A0081194 "A Randomized, Double-Blind, Placebo-controlled, Parallel Group, Multi-center Trial of Pregabalin Controlled Release Formulation as Adjunctive Therapy in Adults with Partial Onset Seizures".

Review:

As the assigned reviewer for this consultation, I attended several of the labeling meetings for this NDA to participate in the discussion. I summarize the DNP recommendations as follows.

Study A0081194 failed to meet its primary efficacy endpoint. (b) (4)

(b) (4) The Sponsor did propose to include information about the study in Section 14 of the label as shown below:

14.3 Adjunctive Therapy for Adult Patients with Partial Onset Seizures

Efficacy has not been established for LYRICA CR as adjunctive therapy in adults with partial onset seizures. (b) (4) (b) (4)

(b) (4)

(b) (4)

(b) (4)

Philip H. Sheridan, M.D.
Medical Reviewer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILIP H SHERIDAN
09/08/2017

TERESA J BURACCHIO
09/08/2017

ERIC P BASTINGS
09/11/2017



MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 8, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D. Acting Director
Martin S. Rusinowitz, M.D., Senior Medical Officer
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Shalini Bansil, M.D., Medical Officer
Controlled Substance Staff

Subject: Pregabalin extended release (ER) tablets; NDA 209501
Trade Name Lyrica CR extended release tablets for oral use
Dosages: 165 mg- 660mg/day; once daily
IND Number: 107333
Indication(s):

- Neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- Postherpetic neuralgia (PHN)
- Fibromyalgia

Sponsor: Pfizer, Inc.
PDUFA Goal Date: October 15, 2017

Materials Reviewed:

- 1.11.4 Abuse related information
- 2.3 Quality overall summary
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
- 2.7.4 Summary of Clinical safety
- 5.3.1 Reports of Biopharmaceutic Studies
- 5.3.5 Reports of efficacy and safety studies
- 1.11.3 Response to FDA request for information, July 28, 2017.
- 1.14 Labeling
- CSS review, K Bonson; NDA 21446, Pregabalin; DARRTS, March 31, 2004

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I. Summary

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) dated January 10, 2017, to evaluate abuse-related data submitted by Pfizer, Inc. in NDA 209501 (developed under IND107333) for Lyrica CR, Pregabalin extended release (ER) tablets. The proposed indications are for 1) management of neuropathic pain associated with

diabetic peripheral neuropathy, 2) management of postherpetic neuralgia, and 3) management of fibromyalgia.

To-be-marketed Pregabalin ER tablets will include 82.5 mg, 165 mg, and 330 mg ER tablets. Pregabalin ER tablets are intended to be administered once daily after an evening meal as 1 to 3 tablets to cover a dose range of 82.5 mg to 660 mg.

Pregabalin has analgesic and anticonvulsant activity, which is thought to be mediated through selective binding to the alpha2-delta subunit of voltage-gated calcium channels in the central nervous system. In the United States (U.S.), pregabalin is currently indicated for use in adults for: 1) neuropathic pain associated with diabetic peripheral neuropathy, 2) postherpetic neuralgia (PHN), 3) neuropathic pain associated with spinal cord injury, 4) fibromyalgia, and 5) as adjunctive treatment for partial onset seizures. Pregabalin is approved as immediate release (IR) oral capsules in various strengths ranging from 25 mg to 300 mg per tablet, and as oral solution formulations at a strength of 20 mg/mL. Recommended dosing of pregabalin ranges from 150 mg to 600 mg/day given in equally divided doses twice or three times a day depending upon the specific indication. Pregabalin extended release (ER) tablets have been developed to support once daily administration following the evening meal. Convenience of once daily administration of pregabalin is expected to enhance patient compliance compared to the IR formulations (capsule and oral solution). To achieve a QD dosing regimen for pregabalin, a controlled-release (CR) formulation which is administered following consumption of food was developed. A conventional CR formulation (i.e., one not administered following food consumption and presumably not retained in the stomach) might not enable QD dosing due to less efficient absorption of pregabalin distal to the ascending colon.

Pregabalin was initially approved in the U.S. in 2004. Pregabalin is a Schedule V controlled substance under the Controlled Substances Act (CSA).

2. Conclusions

- The abuse-related adverse event (AE) profile of the pregabalin CR formulation is similar to the IR formulation in terms of rates of euphoria and somnolence.
- Pregabalin is a Schedule V substance under the CSA and the Sponsor proposes to maintain the current scheduling for the CR formulation.
- However, based on epidemiological studies conducted since the approval of pregabalin and gabapentin, it is clear that the abuse of pregabalin and gabapentin is increasing, especially in individuals who abuse opioids.
- Post-marketing data suggest that pregabalin is commonly co-prescribed with an opioid for the management of pain and to patients in an opioid maintenance treatment program. These data also suggest that use of pregabalin increases mortality in association with opioids.

3. Recommendations (to be conveyed to Sponsor).

1. Based on the profile of effects in human studies following pregabalin products, including Pregabalin ER tablets administration and withdrawal, CSS agrees with the Sponsor's request to maintain Pregabalin ER in Schedule V of the CSA.

2. Labeling changes: CSS has reviewed the labeling provided by the Sponsor under the NDA submission in Module 1.14 and has the following recommendations. Recommended additions are indicated in bold underlined text whereas deletions have been stricken through.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LYRICA CR **contains pregabalin** a Schedule V controlled substance.

9.2 Abuse

Carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA CR misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, immediate release LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of immediate release LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

Epidemiological studies suggest that pregabalin is being abused for the purposes of obtaining a euphoric effect. These epidemiological studies also show that abuse of pregabalin is more common in individuals who abuse opioids. This type of concomitant abuse can lead to increased mortality. Reserve concomitant use of opioids and Lyrica CR for patients with inadequate alternative treatment options, limit to minimum required dosage and duration.

9.3 Dependence

In clinical studies, following abrupt or rapid discontinuation of LYRICA CR, some patients reported symptoms including insomnia, nausea, headache diarrhea, or anxiety [see Warnings and Precautions (5.7)], consistent with physical dependence. In the postmarketing experience with immediate release LYRICA, in addition to these reported symptoms there have also been reported cases of hyperhidrosis.

3. Post marketing requirements: Conduct post marketing studies on the abuse of pregabalin with and without associated abuse of opioids as described by the Office of Surveillance and Epidemiology (OSE). The objectives of these studies are to understand the extent of off-label use, and to capture data on the misuse and abuse of ER pregabalin, and their clinical consequences, in both long-term and short-term users. The risks associated with the use of pregabalin, with and without concomitant use of opioid analgesics, and the risk factors for nonmedical use of pregabalin are not entirely clear. More and better quality data are needed to understand the public health burden associated with pregabalin, and post-market required studies are a vehicle to generate necessary safety data in this area.

2.1 Receptor Binding and Functional Assays

A. Receptor Binding

Pregabalin does not have a receptor binding profile that is similar to any known drugs of abuse, nor does it bind significantly to any major or minor neurotransmitter system in the brain with the exception of the calcium channel. This is similar to the binding profile for gabapentin. The mechanism of action of pregabalin is not well understood. (Summarizing from CSS review by K Bonson, March 31, 2004, NDA 21446 DARRTS).

B. Microdialysis in Rats

Morphine increased extracellular levels of dopamine in the nucleus accumbens, but pregabalin and saline did not. Pregabalin blocked the increase in dopamine following morphine administration. Since dopamine levels are increased by many, but not all, drugs of abuse, this suggests that pregabalin does not have the same reinforcing effects as morphine, a Schedule II drug. (Summarizing from CSS review by K Bonson, March 31, 2004, NDA 21446 DARRTS).

2.2 Animal Behavioral Studies

The preclinical behavioral studies with pregabalin were assessed by CSS to not be valid for assessing abuse potential. Despite inadequately designed preclinical studies, there are indications in the preclinical studies that pregabalin has abuse potential: pregabalin produced self-administration of >10 injections/day at the 3.2 and 10 mg/kg/infusion doses during initial access to the drug, thus demonstrating that pregabalin produces reinforcing effects. (Summarizing from CSS review by K Bonson, March 31, 2004, NDA 21446 DARRTS).

2.3 Tolerance and Physical Dependence Studies in Animals

Rats received pregabalin (100-400 mg/kg, i.p.) or pentobarbital (up to 900 mg/kg, i.p.) for 12 days. The doses chosen were based on minimum effective dose 40 times that for anxiolysis/analgesia. The withdrawal signs that were counted included changes in body weight and hyperexcitability. Weight loss during drug discontinuation showed a 3% loss in placebo group, a 14% loss in the pentobarbital group, and a 10-11% loss in the pregabalin group.

Another measure was "cumulative signs in 96 hr", with the vehicle group showing a score of 1, the pentobarbital group at score of 14, and the pregabalin group a score of 4-6.

These data show a mild withdrawal syndrome following discontinuation of pregabalin (Summarizing from CSS review by K Bonson, March 31, 2004, NDA 21446 DARRTS).

3. Clinical Pharmacology

Clinical pharmacology studies evaluating pilot pregabalin ER formulations supported [REDACTED] (b) (4) [REDACTED] account for variation in relative bioavailability compared with the IR formulation. Pregabalin ER demonstrates linear PK with dose-proportional increases in total daily exposures (AUC₂₄), C_{max}, and C_{min} from 82.5 to 660 mg QD.

Pregabalin ER tablets administered QD following the evening meal demonstrate equivalent AUC₂₄ exposures relative to a comparative dose of pregabalin IR capsules administered without food 2 or 3 times daily.

C_{max} and C_{min} for pregabalin ER administered QD following the evening meal were approximately 63% to 68% and 73% to 84%, respectively, of comparative doses of pregabalin IR capsules administered without food every 12 hours (q12h). T_{max} for pregabalin CR is 5-12 hours and for pregabalin IR is 0.7-1.5 hours.

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

When administered QD following an evening meal, pregabalin ER tablets have sustained absorption with C_{max} occurring approximately 8 to 10 hours postdose. Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin clearance is nearly proportional to CL_{cr}. Dosage reduction in patients with reduced renal function is necessary.

3.2 Drug/Product Interactions

Pregabalin ER tablets are recommended to be administered QD following the evening meal. The bioavailability of pregabalin ER tablets is reduced if taken on an empty stomach. AUC decreases approximately 30% when the pregabalin ER tablet is administered fasted relative to administration following an evening meal.

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin. Additive effects on cognitive and gross motor functioning were seen when pregabalin was co-administered with ethanol, lorazepam, or oxycodone.

4. Clinical Studies

4.1 Adverse Event Profile Through all Phases of Development

The safety information included in this NDA was obtained from the 12 completed Phase 1 studies and 3 Phase 3 controlled studies (Study 1224 [PHN], Study 1245 [FM], and Study 1194 [epilepsy] using the pregabalin ER proposed commercial tablet formulation.

Phase 1 studies:

A0081188 (Phase 1): An Open-Label, Single-Dose, Randomized, Four-Way Crossover Study in Healthy Volunteers to Investigate the Pharmacokinetics of Pregabalin Controlled Release Formulation Administered at Lunch Following Various Caloric Intakes as Compared to the Immediate Release Formulation

The study was designed to evaluate the effect of caloric intake on the single dose PK of a 330-mg commercial image pregabalin CR tablet administered following lunch relative to the single dose PK of the IR capsule (reference formulation) administered fasted. Twenty-eight (28) subjects were randomized. The most frequently reported AEs were balance disorder, dizziness, somnolence, and

euphoric mood. Somnolence was reported in 5% of individuals who were in the CR group and 11% in the IR group. Euphoric mood was reported in 7.5% of the CR group and 18.5% of the IR group

A0081198 (Phase 1): An Open-Label, Multiple-Dose, Randomized, 3-Way Crossover Study in Healthy Volunteers to Determine the Steady-State Pharmacokinetics of the 165 mg and 330 mg Dose Strengths of Pregabalin Controlled Release Formulations Administered Following an Evening Meal and 150 mg of the Immediate Release Formulation Administered Twice Daily. The purpose of this study was to evaluate the steady-state PK and the equivalence of the extent of absorption of the 330-mg commercial image pregabalin CR formulation administered QD immediately following an evening meal relative to the steady-state fasted PK of the 150-mg IR formulation administered BID. An additional objective of this study was to evaluate the steady-state PK and the equivalence of the extent of absorption of 2 tablets of the 165-mg (ie, 330 mg) commercial image pregabalin CR formulation relative to the 330-mg commercial image CR formulation. Subjects received in a randomized sequence total daily oral doses of 330 mg of the CR formulation (2 tablets of the 165-mg CR formulation administered concurrently), 330 mg of the CR formulation (1 tablet of the 330-mg CR formulation), and 300 mg of the IR formulation. For each period, subjects were housed as inpatients from Day 1 through the 24-hour PK assessment on Day 5. Twenty four (24) subjects were assigned to study treatment. In the CR group 34% reported somnolence and in the IR group 29% reported somnolence. Four percent of individuals reported euphoric mood in both the IR and CR groups.

A0081215 (Phase 1): An Open-Label, Multiple-Dose, Randomized, 2-Way Crossover Study in Healthy Volunteers to Determine the Steady-State Pharmacokinetics of the 82.5 mg Pregabalin Controlled Release Formulation Administered Following An Evening Meal Relative to the 25 mg of the Immediate Release Formulation Administered Three Times Daily. The study was designed to evaluate the steady-state PK and the equivalence of the extent of absorption of the 82.5 mg commercial image CR tablet administered QD following the evening meal relative to the steady-state fasted PK of 25 mg of the IR formulation administered TID. Subjects received in a randomized sequence total daily oral doses of 82.5 mg of the CR formulation and 75 mg of the IR formulation for a total of 4 days. A total of 18 subjects were randomized to open-label treatment. One individual in the CR group reported hypersomnia.

A0081216 (Phase 1): An Open-Label, Multiple-Dose, Randomized, 2-Way Crossover Study in Healthy Volunteers to Determine the Steady-State Pharmacokinetics of 660 mg (2 × 330 mg Tablets) Pregabalin Controlled Release Formulation Administered Following an Evening Meal Relative to the 300 mg of the Immediate Release Formulation Administered Twice Daily. The current study was designed to evaluate the steady state PK and the equivalence of the extent of absorption of two 330-mg (ie, 660 mg) commercial-image CR tablets administered concurrently QD immediately following an evening meal relative to the steady-state fasted PK of 300 mg of the IR formulation administered every 12 hours. This study was an open-label, multiple-dose, randomized, 2-period, 2-treatment crossover study in 18 healthy adult volunteers between the ages of 18 and 55 years. The most frequently reported AEs were feeling drunk (12 of 18 in CR group and 7 of 18 in the IR group), fatigue, headache, dizziness, visual impairment, and head discomfort. Euphoric mood was reported in 2 of 18 in the CR group and 0 of 18 in the IR group.

A0081225 (Phase 1): An Open-Label, Multiple-Dose, Randomized, Crossover Study in Healthy Volunteers to Investigate the Pharmacokinetics of Three Dose Strengths of Pregabalin Controlled

Release Formulations Administered Following an Evening Meal as Compared to the Immediate Release Formulation. This study was an open-label, multiple-dose, randomized, 4-period, 4-treatment, cross-over study in 20 healthy adult volunteers. Subjects received in a randomized sequence total daily oral doses of 82.5 mg CR, 165 mg CR, 330 mg CR, and 300 mg of the IR formulation. The most commonly reported AEs were fatigue, dizziness and somnolence. Somnolence was reported in 13 of 60 (22%) subjects of the CR group and in 3 of 20 (15%) of the IR group.

A0081226 (Phase 1): An Open-Label, Multiple-Dose, Randomized, 3-Way Crossover Study in Healthy Volunteers to Determine the Steady-State Pharmacokinetics of the 82.5 mg and 165 mg Dose Strengths of Pregabalin Controlled Release Formulations Administered Following an Evening Meal and 75 mg of the Immediate Release Formulation Administered Twice Daily. The study was designed to evaluate the steady-state PK and the equivalence of the extent of absorption of the 165-mg commercial image CR tablet administered QD immediately following the evening meal relative to the steady-state fasted PK of 75 mg of the IR formulation administered every 12 hours. An additional objective of this study was to evaluate the steady-state PK and the equivalence of the extent of absorption and peak concentrations of 2 tablets of the 82.5-mg (ie, 165 mg) commercial image CR formulation administered concurrently QD immediately following the evening meal relative to the 165-mg commercial image CR tablet. This study was an open-label, multiple-dose, randomized, 3-period, 3-treatment, 6-sequence crossover study in 24 healthy adult volunteers. The most frequently reported AEs in the SOC of nervous system disorders were dizziness, hypersomnia, somnolence, and headache. Hypersomnia and somnolence were reported in 12 (25%) and 7(15%) of 47 subjects in the CR group, respectively and in 3 (12.5) and 2 (8.3%) of 24 subjects in the IR group, respectively. Euphoric mood was reported in 2 subjects in the CR group and none in the IR group.

Protocol A0081227 (Phase 1): An Open-Label, Single-Dose, Randomized, Four-Way Crossover Study in Healthy Volunteers to Evaluate the Effects of a Low, Medium and High Fat Evening Meal on the Pharmacokinetics of Pregabalin Controlled Release Formulation as Compared to the Immediate Release Formulation. The purpose of the study was to evaluate the effect of a low-, medium- and high-fat meal content, 800 to 1000 calorie evening meal, on the single dose PK of a 330 mg commercial image pregabalin CR tablet relative to the single dose PK of the IR (reference) capsule formulation administered following a medium-fat 800 to 1000 calorie evening meal. This study was an open-label, single dose, randomized, 4-period, 4-sequence, crossover study in 28 healthy adult volunteers. One subject was discontinued from the study as he tested positive for cocaine. Most frequently reported AEs were dizziness, balance disorder, fatigue, headache, somnolence, and euphoric mood. Somnolence was reported by 8 of 83 (9.6%) CR subjects and 2 of 27(7.4%) IR subjects. Euphoric mood was reported by 3 of 83 CR subjects (3.6%) and 3 of 27 IR subjects(11%).

A0081228 (Phase 1): The Pharmacokinetics of Pregabalin Controlled Release Formulation in Fed State Compared to the Controlled Release and Immediate Release Formulations in the Fasted State. The study was designed to evaluate the absorption, PK, and safety of a single dose of a 330-mg commercial-image pregabalin CR tablet administered in the evening under fasted and fed conditions. Additionally, the results of the 2 CR treatments were compared to a single dose of the 300-mg IR formulation administered fasted. This study was an open-label, single-dose, randomized, 3-period, 3-treatment, 6-sequence crossover study in 24 healthy adult volunteers. Two subjects were lost to follow up for unclear reasons. The most frequently reported AEs were dizziness, fatigue, somnolence, and headache. Eight of

47(17%) in the CR group reported somnolence and 1 of 23 (4.3%) in the IR group reported somnolence. Euphoria was reported in 2% of CR subjects and 4% of IR subjects.

A0081238 (Phase 1): An Open-Label, Single-Dose, Randomized, Four-Way Crossover Study in Healthy Volunteers to Evaluate the Effects of Caloric Content and Time of Dosing on the Pharmacokinetics of Pregabalin Controlled Release Formulation as Compared to the Immediate Release Formulation. This study was designed to evaluate the single-dose PK of a 330-mg commercial-image pregabalin CR formulation administered: 1) immediately following a 400- to 500-calorie medium-fat evening meal; 2) immediately following a 600- to 750-calorie medium-fat evening meal; and 3) at bedtime approximately 4 hours following completion of a 600- to 750-calorie medium-fat meal relative to 300 mg of the IR formulation administered fasted in the evening. This was an open-label, single-dose, randomized, 4-period, 4-sequence, crossover study in 24 healthy adult volunteers. The most frequently reported AEs were dizziness, euphoric mood, and feeling abnormal. Euphoric mood was reported in 8 of 69 (11.5%) subjects in the CR group and 1 of 22 in the IR group (4.5%).

A0081239 (Phase 1): An Open-Label, Single-Dose, Randomized, Four-Way Crossover Study in Healthy Volunteers to Investigate the Pharmacokinetics of Pregabalin Controlled Release Formulation Administered Following Various Caloric Intakes as Compared to the Immediate Release Formulation. This study was designed to evaluate the effect of caloric intake on a single dose PK of a 330-mg pregabalin CR tablet administered following breakfast, relative to the single dose PK of the IR capsule administered in the fasted state. This study was an open-label, single-dose, randomized, 4-period, 4-sequence, crossover study in 24 healthy adult subjects. Somnolence was reported by 11 of 70 (15.7%) subjects in the CR group and 7 of 23 (30%) in the IR group. Euphoric mood was reported by 2 of 70 (2.8%) in the CR group and 1 of 23 (4.3%) in the IR group.

Table 1. Abuse related AEs in Phase 1 studies (NDA 209501) Pregabalin IR vs CR formulations

Abuse related AE	Pregabalin CR; n= 520	Pregabalin IR; n= 208
Feeling abnormal	10(2%)	4 (2%)
Euphoria	31 (5.9%)	12 (5.7%)
Feeling drunk	19 (3.6%)	16 (7.6%)
Somnolence	70 (13.4%)	29 (13.9%)

Phase 3 studies:

A0081224 A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of Once Daily Controlled Release Pregabalin in the Treatment of Patients with Postherpetic Neuralgia: The purpose of this study was to evaluate the efficacy and safety of pregabalin CR administered QD as compared to placebo in the treatment of PHN. The present study used a randomized withdrawal (RW) study design. The RW design included 2 phases:

- A single-blind (SB) pregabalin CR treatment phase, and
- A double-blind (DB) RW phase.

Subjects who responded to pregabalin CR in the SB phase (with at least 50% improvement in pain at the end of SB phase as compared to pretreatment baseline) were considered for

participation in the DB phase. Eligible subjects were then randomly assigned to continue pregabalin CR or to “withdraw” to placebo in the DB phase. A total of 1117 subjects were screened for inclusion in the SB phase of the study of which 801 subjects received at least 1 dose of SB pregabalin CR 82.5 to 330 mg/day (subjects with low baseline CLcr) or SB pregabalin CR 165 to 660 mg/day (subjects with normal baseline CLcr). A total of 418 subjects (51.5%) were randomized, and 413 subjects received at least 1 dose of DB treatment; 208 subjects received pregabalin CR 82.5 to 660 mg/day and 205 subjects received placebo. The median duration of treatment (including taper) in the SB phase was 42.0 days with 715 (89.3%) subjects treated for at least 29 days. The median duration of treatment (including taper) in the DB phase was 91.0 days and 90.0 days in the pregabalin CR and placebo groups, respectively. Somnolence was reported in 92 of 801 (11.4%) pregabalin treated subjects and none in placebo subjects. Euphoric mood was reported in 3 of 801(0.4%) pregabalin treated subjects. In 3 subjects there was a report of missing tablets.

A0081245 A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of Once Daily Controlled Release Pregabalin in the Treatment of Patients with Fibromyalgia: The present study used a RW study design.

The RW design included 2 phases:

- A SB pregabalin CR treatment phase, and;
- A DB randomized withdrawal phase.

Subjects who responded to pregabalin CR in the SB phase (with at least 50% improvement in pain at the end of SB as compared to pretreatment baseline) were considered for participation in the DB phase.

Eligible subjects were then randomly assigned to placebo or to continue pregabalin CR. The study consisted of 4 phases:

1. Baseline (1 week);
2. Single-blind (6 weeks);
3. Double-blind treatment (13 weeks);
4. Taper (1 week). The subjects received the following doses of study medication, taken orally within 1 hour of the evening meal.
 - Pregabalin CR 165 mg;
 - Pregabalin CR 330 mg;
 - Pregabalin CR 495 mg;
 - Matching placebo.

A total of 770 subjects were screened for inclusion in the SB phase of the study of which 441 received at least 1 dose of pregabalin CR 165 - 495 mg/day.

A total of 122 subjects were randomized, and 121 subjects received at least one dose of DB treatment (63 subjects received pregabalin CR 330 - 495 mg/day and 58 subjects received placebo.

In the SB phase, the most common AEs, by PT, were dizziness (161 [36.5%] subjects), somnolence (105 [23.8%] subjects), headache (43 [9.8%] subjects), fatigue (42 [9.5%] subjects), and nausea (41 [9.3%] subjects). In the DB phase, for subjects treated with pregabalin CR the most common AEs by PT were peripheral edema (6 [9.5%] subjects), nausea (5 [7.9%] subjects), and insomnia (3 [4.8%] subjects). No euphoria or somnolence was noted during the double blind phase. During the single blind phase of 441 subjects 3 (0.7%) reported feeling drunk, 105(24%) reported somnolence, 2(0.5%) affect lability, and 10 (2.3%) euphoria. Nineteen (4.3%) reported feeling abnormal.

A0081194 A Randomized, Double-Blind, Placebo-controlled, Parallel Group, Multi-center Trial of Pregabalin Controlled Release Formulation as Adjunctive Therapy in Adults with Partial Onset Seizures (Phase 3). The primary objective of this study was to evaluate the efficacy of 2 different dosages of pregabalin CR administered once daily as compared to placebo as adjunctive treatment in reducing the frequency of seizures in partial onset epilepsy. This study was a randomized, double-blind, 3 arm parallel-group, placebo-controlled, multicenter, multinational study in subjects requiring additional treatment for partial onset seizures. A total of 400 subjects were screened for inclusion in this study, of which 325 subjects were assigned to a treatment group (pregabalin CR 165 mg: 101 subjects; pregabalin CR 330 mg: 114 subjects; placebo: 110 subjects). The median duration was 105 days for subjects in each treatment group Somnolence was reported in 10 of 213 pregabalin treated patients (4.6%) and 2 of 110 (1.8%) placebo patients.

Table 2. Abuse related AEs in Phase 3 studies (NDA 209501) during single blind phase Pregabalin CR

Abuse related AE	Pregabalin CR; n= 1242
Mood alteration	6 (0.5%)
Euphoria	13 (1.04%)
Feeling drunk	3 (0.2%)
Somnolence	196 (16%)

Table 3. Abuse related AEs in Phase 3 studies (NDA 209501) during double blind phase Pregabalin vs placebo

Abuse related AE	Pregabalin CR; n=484	Placebo; n=373
Somnolence	11 (2.3%)	2 (0.5%)
Euphoria	0	0

4.2 Safety Profile

All integrated AE data analyses were performed using unique preferred terms (PTs) included in Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or above.

Across Phase 1 multiple dose pregabalin ER studies the most common AEs (incidence >10% overall) were dizziness (41 subjects [39.4%]), fatigue (37 subjects [35.6%]), hypersomnia (27 subjects [26.0%]), headache, somnolence (each with 25 subjects [24.0%]), insomnia (17 subjects [16.3%]), and feeling drunk (16 subjects [15.4%]). Dizziness was the most common AE in the pregabalin ER 330 mg QD treatment group (32 subjects [72.7%]) and feeling drunk was the most common AE in the pregabalin ER 660 mg QD treatment group (12 subjects [66.7%]). Euphoric mood was reported in 5.8% of subjects and was dose dependent.

In the Phase 3 studies for all pregabalin ER doses combined, dizziness (22.4%), somnolence (14.2%), fatigue (5.9%), peripheral edema (5.6%), headache (5.6%), nausea (5.5%), vision blurred (4.7%), weight increased (4.7%), and dry mouth (4.1%) were the most common frequently reported AEs. Feeling

abnormal was reported in 1.5% and sedation in 1% individuals. In Phase 3 studies, the overall incidence of euphoric mood with pregabalin ER was 0.9% (13/1455 subjects).

Overall, the incidence of euphoric mood was similar for pregabalin ER as compared with Phase 2 and 3 clinical studies with pregabalin IR for PHN (0.6%), NeP associated with DPN (0.9%), and FM (5.6%). No events of drug abuse and dependence were identified in the narrow SMQ search strategy.

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

No events of drug abuse and dependence were identified in the narrow SMQ search strategy. In the Phase 3 study on PHN, there were reports of missing tablets in 3 subjects. There were no other drug accountability issues in the other trials.

4.4 Tolerance and Physical Dependence Studies in Humans

A narrow MedDRA SMQ on drug withdrawal was used to search the pregabalin ER clinical studies databases for potential cases suggestive of possible drug withdrawal and rebound symptoms. One case of drug withdrawal headache was reported during the SB phase of PHN study. No other events related to withdrawal and rebound were retrieved from the pregabalin ER Phase 3 clinical studies databases using the same search criteria. In the Phase 3 pain studies, following abrupt or rapid discontinuation of pregabalin ER treatment, 5 symptoms potentially related to discontinuation were reported as follows: anxiety (2 cases), insomnia (4 cases), nausea (5 cases), headache (1 case), or diarrhea (2 cases). These events were reported during the 3 days following the 1-week taper period following the SB phase or 3 days after the 1-week taper following the DB phase. These symptoms are similar to what was reported in the clinical trials with pregabalin IR capsules.

As a result, it is recommended that discontinuing treatment with pregabalin ER include a taper gradually over a minimum of 1 week to avoid AEs associated with discontinuation of treatment.

5. Other Relevant Information

CSS sent an information request to the Sponsor to provide AEs related to the prior and concomitant use of opioids in all pregabalin studies (IR and CR). The Sponsor submitted the AEs by SOC and PT. The tables below show treatment emergent AEs occurring during the pregabalin clinical studies for subjects with any opioid use prior to the initiation of study treatment. Medications taken within 30 days of the start of study treatment were typically reported, with a longer recall period for some of the more recent studies. The concomitant opioid use tables reflect AEs occurring on or after the first date of opioid usage. The PHN (ER and IR) and NeP-SCI studies (IR) allowed concomitant opioid use. For the other studies, concomitant opioid use was prohibited. The following tables are representative of cardiopulmonary AEs reported with concomitant and prior opioid use in the Phase 3 studies.

Table 4. Adverse Events for subjects with Prior Opioid use - IR Controlled Studies, Parallel Group Design

AE	Pregabalin; n=786	Placebo; n=341
Dyspnea	9 (1.1%)	5(1.5%)
Bradycardia	1(0.1%)	0 (0.0%)

Table 5. Adverse Events for subjects with Concomitant Opioid use - IR Controlled Studies, Parallel Group Design

AE	Pregabalin; n=407	Placebo; n=211
Dyspnea	6 (1.5%)	3(1.4%)
Bradycardia	1(0.2%)	0 (0%)

Table 6. Adverse Events for subjects with Prior Opioid use - IR Controlled Studies, Randomized Withdrawal Design, All Pregabalin Subjects

AE	Pregabalin; n=217
Dyspnea	3 (1.4%)

Table 7. Adverse Events for subjects with Prior Opioid use - Double Blind Phase Pregabalin ER studies

AE	Pregabalin; n= 37	Placebo; n=25
Bundle branch block left	1(2.7%)	0 (0%)

In response to another information request from CSS, the Sponsor submitted postmarketing reports (PMRs) on respiratory depression, cardiac arrhythmias, and deaths associated with the concomitant and prior use of opioids with Lyrica IR. Among 15579 PMRs, 69 cases of respiratory depression, 597 cardiac arrhythmias, and 247 deaths were reported. CSS reviewed the 69 cases of respiratory depression. After excluding individuals with comorbidities such as cancer, respiratory and cardiac disease, and individuals with concomitant benzodiazepine use, there were 7 (10%) individuals who appeared to have suffered respiratory depression due to concomitant Lyrica and opioid use. Respiratory depression occurred within 2-15 days of starting Lyrica IR. The reports indicate that opioid use was not new, the dose of Lyrica was therapeutic, and all subjects were female.

Literature Review:

CSS has conducted a review of the recent literature (2014-2017) on pregabalin and gabapentin (gabapentinoid) abuse. The number of gabapentin and pregabalin prescriptions has been steadily increasing since 2012 in the US.¹ Epidemiological studies and case reports indicate that individuals are administering higher than recommended doses to achieve euphoria.² Gabapentinoid abuse prevalence is higher in opioid users than in the general population (3-68% vs 1.6%)². Fatalities associated with gabapentinoid abuse usually occur in association with opioid use.^{3,4} In a study of heroin users, the participants indicated that pregabalin reinforced the effects of heroin, that the combination caused ‘blackouts,’ and increased the risk of overdose.⁴ Studies in animals and humans suggest that gabapentinoids may have an additive effect on opioid induced respiratory depression or may depress respiration by reversal of opioid tolerance.^{4,5} CSS requested an OSE consult to evaluate the postmarketing abuse of pregabalin (NDA 209501, DARRTS; March 24, 2017).

OSE consult:

Conclusions: Pregabalin is a controlled substance with a known abuse potential. Post-marketing data suggest that pregabalin is misused and abused alone, and in combination with opioid analgesics and

Medication-assisted treatment (MAT) products for treatment of opioid use disorder. The consequences of misuse or abuse of pregabalin, with or without opioid analgesics or MAT products, is associated with fatalities. Utilization of pregabalin is increasing, albeit modestly, but the impact of the introduction of an ER pregabalin product to the market is unclear. Given the uncertainty in how the new pregabalin ER formulation will impact on therapeutic use of pregabalin overall, that the abuse of ER pregabalin is likely, and that pregabalin products may be prescribed concomitantly with opioid analgesics, DEPI recommended considering post-market required studies as condition of approval of ER pregabalin to understand the risks associated with the use of ER pregabalin with and without concomitant opioid analgesics. Post-market required studies should be considered for the IR pregabalin, as well as gabapentin products, given their similarities with pregabalin products in indication, utilization, and post-market reporting of abuse and misuse, and their consequences. DEPI also recommends considering enhanced warnings in the label for all pregabalin and gabapentin products regarding the risks of misuse, abuse, addiction, overdose and death, and the risks associated with concurrent opioid use (analgesic and MAT). CSS concurs with these recommendations.

6. Regulatory Issues and Assessment

Pregabalin ER plasma PK characteristics are not expected to appreciably influence the abuse potential of pregabalin. Pregabalin ER has the same total daily exposures relative to the comparative dose of IR. Additionally, peak concentrations are lower and time to peak concentrations are delayed with pregabalin ER relative to pregabalin IR (maximum plasma drug concentration [C_{max}]; 63-68% with pregabalin ER QD relative to pregabalin IR twice a day (BID); (time to maximum plasma drug concentration [t_{max}]; 8-10 hours with pregabalin ER and approximately 1.5 hours with pregabalin IR). In addition the proposed Pregabalin ER strengths (82.5 mg, 165 mg, and 330 mg) overlap with currently marketed IR strength, thus even if upon manipulation of the ER tablets it were possible to release the entire amount of pregabalin present in the ER formulation, the amount of pregabalin release would not be higher than the amount of pregabalin available in its IR version.

The abuse-related AE profile of the CR formulation is similar to the IR formulation in terms of rates of euphoria and somnolence. Pregabalin is a Schedule V substance under the Controlled Substances Act and the Sponsor proposes to maintain the current scheduling for the CR formulation.

However, based on epidemiological studies, conducted since the approval of pregabalin and gabapentin, it is clear that the abuse of pregabalin and gabapentin is increasing, especially in individuals who also abuse opioids. Phase 3 studies in the pregabalin IR and CR development programs did not reveal AEs related to the concomitant use of opioids and pregabalin. This may be related to the relatively small number of patients with concomitant use and the rigorous environment of controlled studies. Pregabalin is commonly co-prescribed with an opioid for the management of pain and to patients in an opioid maintenance treatment program. Pregabalin may enhance respiratory depression and increase mortality in association with opioids. The labeling for Lyrica CR should address the increasing abuse of pregabalin and include an enhanced warning about the concomitant use of opioids.

Additionally, the Sponsor should conduct post marketing studies on the abuse of pregabalin with and without the use of opioids.

Labeling Recommendations for Section 9 DRUG ABUSE AND DEPENDENCE:

9.1 Controlled Substance

LYRICA CR **contains pregabalin** a Schedule V controlled substance.

9.2 Abuse

Carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA CR misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, immediate release LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of immediate release LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

Epidemiological studies suggest that pregabalin is being abused for the purposes of obtaining a euphoric effect. These epidemiological studies also show that abuse of pregabalin is more common in individuals who abuse opioids. This type of concomitant abuse can lead to increased mortality. Reserve concomitant use of opioids and Lyrica CR for patients with inadequate alternative treatment options, limit to minimum required dosage and duration.

9.3 Dependence

In clinical studies, following abrupt or rapid discontinuation of LYRICA CR, some patients reported symptoms including insomnia, nausea, headache diarrhea, or anxiety [see Warnings and Precautions (5.7)], consistent with physical dependence. In the postmarketing experience with immediate release LYRICA, in addition to these reported symptoms there have also been reported cases of hyperhidrosis.

III. References.

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4. Lyndon A. Risk to heroin users of polydrug use of pregabalin or gabapentin. Addiction. Sep 2017; 1580.
5. Myhre M. Pregabalin has analgesic, ventilatory, and cognitive effects in combination with remifentanyl. Anesthesiology. Jan 2016; 141.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 7, 2017

To: Sharon Hertz, MD
Director
**Division of Anesthesia, Analgesia, and
Addiction Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

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Acting Team Leader, Patient Labeling
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From: Morgan Walker, PharmD, MBA, CPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

LaToya Toombs, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): LYRICA CR (pregabalin)

Dosage Form and Route: extended-release tablets, for oral use, CV

Application Type/Number: NDA 209501

Applicant: Pfizer Inc.

1 INTRODUCTION

On December 15, 2016, Pfizer Inc. submitted for the Agency's review a New Drug Application (NDA) 209501 for LYRICA CR (pregabalin) extended-release tablets. The proposed indication is:

- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Management of fibromyalgia

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on February 3, 2017, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LYRICA CR (pregabalin) extended-release tablets.

2 MATERIAL REVIEWED

- Draft LYRICA CR (pregabalin) extended-release tablets MG received on December 15, 2016, and received by DMPP and OPDP on August 17, 2017.
- Draft LYRICA CR (pregabalin) extended-release tablets Prescribing Information (PI) received on December 15, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 17, 2017.
- Approved LYRICA (pregabalin) comparator labeling dated December 22, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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09/07/2017

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09/07/2017

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Department of Epidemiology II**

**Epidemiology Review: Pregabalin use and abuse with and without
concurrent opioid use**

Date: 9/7/2017

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Office of Surveillance and Epidemiology (OSE)

Subject: A review of data and literature relevant to pregabalin use and abuse, and an assessment of the frequency and consequences of concurrent use or abuse of opioids and pregabalin

Drug Name(s): Lyrica CR (pregabalin ER)
Sponsor: Pfizer, Inc.
Application Type/Number: NDA 209501
OSE RCM #: 2017-619

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

The Controlled Substance Staff (CSS) in the Office of the Center Director requested that the Division of Epidemiology (DEPI) review relevant literature and provide epidemiological data on pregabalin use and abuse with and without concurrent opioid use or abuse. This consult was generated in response to an extended-release (ER) pregabalin product currently under review for approval. For comparison, gabapentin was included in all analyses.

Since recent published reports indicate expanding use of all gabapentinoids, DEPI used proprietary drug utilization databases to conduct drug utilization analyses for both pregabalin and gabapentin. DEPI also examined data from the National Poison Data System (NPDS) to evaluate trends in intentional and unintentional exposure calls associated with pregabalin and gabapentin to poison control centers in the U.S. DEPI searched for adverse drug event (ADE) cases in the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES), a data resource capturing ADEs that lead to emergency department (ED) visits in a nationally representative sample of hospitals. Finally, DEPI conducted a comprehensive literature search to identify published data and studies on pregabalin and gabapentin abuse and misuse, and their consequences, with a particular focus on literature discussing concurrent opioid use or abuse.

The total number of prescriptions dispensed for pregabalin increased by (b) (4) from approximately (b) (4) in 2012 to approximately (b) (4) in 2016. In comparison, the number of prescriptions dispensed for gabapentin increased by (b) (4) from approximately (b) (4) in 2012 to (b) (4) in 2016. In 2016, based on an office-based physician survey, pregabalin was mentioned during office visits with the use of opioid analgesics in approximately (b) (4)% of drug occurrences noting pregabalin; gabapentin was mentioned with the use of opioid analgesics in approximately (b) (4)% of drug occurrences noting gabapentin.

Overall, DEPI identified (b) (4) total pregabalin exposure calls between 2005 and 2016, including (b) (4) single-substance exposure calls. Pregabalin exposure calls rose sharply after market approval in 2005, then remained fairly steady after 2008. DEPI identified (b) (4) total gabapentin exposure calls between 2004 and 2016, including (b) (4) single-substance exposures calls. Gabapentin exposure calls decreased from 2004 to 2006, and increased every year from 2007 to 2016. Pregabalin and gabapentin total exposure rates per 100,000 prescriptions dispensed were similar and remained relatively consistent from 2012 to 2016. The rate of concurrent pregabalin and opioid exposure calls per 100,000 pregabalin prescriptions dispensed was also relatively consistent from 2012 to 2016 (ranging from (b) (4) per 100,000 prescriptions dispensed).

Overall, there were large increases in the projected counts of non-abuse-related ED visits for gabapentin from 2005 to 2015, but that may be due to commensurate increases in gabapentin utilization over that time, as evidenced by the utilization-adjusted rates in the last 4 years of that period. For pregabalin, there were slight increases in counts of ED visits from 2012 to 2015 with stable numbers of prescriptions dispensed over that period, resulting in increases in normalized rates (per 100,000 prescriptions dispensed).

The studies identified in the literature search were broadly categorized into three areas: 1) surveys in high risk populations, 2) surveillance of electronic data (registries, administrative claims, poison centers), and 3) drug-involved mortality investigations.

Data from the survey-based investigations suggest that gabapentinoid misuse and abuse is particularly problematic among those who abuse prescription opioids and heroin, and among those in treatment for substance abuse, including medication assisted treatment (MAT). It also appears that the concurrent misuse of gabapentinoids and opioids is primarily to enhance the effect of the opioid.

The studies using electronic data systems appear to suggest that pregabalin use is associated with higher risk of both overdose mortality and all-cause mortality among patients on MAT, and that many patients are dispensed pregabalin and gabapentin above the recommended daily dose range in the U.S. and other developed countries, with and without concomitant opioid dispensing.

Data from the drug-involved mortality studies indicate that gabapentinoids are implicated in drug overdose deaths among those who may be directly abusing the drugs in several developed countries. Mortality rates from overdose involving gabapentinoids may be increasing over time, and opioid analgesics are also noted in a significant proportion of gabapentinoid-involved overdose deaths.

Overall, post-marketing data do suggest that both gabapentinoids are abused and misused, particularly among those who abuse or misuse opioids, and those on MAT. These drugs are abused both alone and simultaneously with opioids, and/or other CNS depressants. While the data are limited, as postmarketing research in this area is still in its nascent stages, it is also possible that the abuse or misuse of gabapentinoids is increasing over time. Abuse of these drugs does not yet appear widespread; nonetheless, utilization of the gabapentinoids continues to increase, most notably for gabapentin, which may also increase their availability for misuse. It is clear that those who abuse opioids or are in treatment for opioid misuse (MAT or otherwise) are at risk of gabapentinoid misuse or abuse, and the consequences can be fatal.

Given the concerns around opioid analgesics, post-market required studies should be considered for ER pregabalin and all other pregabalin products in an attempt to understand the risks associated the use of pregabalin with and without concomitant opioid analgesics. Additionally, enhanced warning about the risks of misuse, abuse, addiction, overdose and death associated with pregabalin, and the risks associated with concurrent pregabalin and opioid use (analgesic and MAT), should be considered for all pregabalin product labels. In regards to gabapentin products, given their similarities with pregabalin products in indication, utilization, and post-market reporting of abuse and misuse, and their consequences, post-market required studies and enhanced labeling are also warranted for gabapentin products and should be considered.

1 INTRODUCTION

The Controlled Substance Staff (CSS) in the Office of the Center Director requested that the Division of Epidemiology (DEPI) review relevant literature and provide epidemiological data on pregabalin use and abuse with and without concurrent opioid use

or abuse. This consult was generated in response to an extended-release (ER) pregabalin product currently under review for approval. This review summarizes relevant data and literature on current pregabalin use and abuse, and what may be expected if the ER product under review is approved for marketing.

1.1 BACKGROUND

Pregabalin (a gabapentinoid) is an anticonvulsant approved in 2004 as adjunct therapy for partial onset seizures in patients with epilepsy, and for the management of neuropathic pain from diabetic peripheral neuropathy and postherpetic neuralgia.ⁱ In 2007, indications for pregabalin were expanded to include pain from fibromyalgia, and again in 2012 to include neuropathic pain associated with spinal cord injury. Potential side effects for pregabalin include angioedema, peripheral edema, hypersensitivity reactions, suicidal thoughts or behaviors, blurred vision, dizziness and somnolence.

In 2005, citing clinical trial data indicating abuse potential, the Drug Enforcement Administration (DEA) assigned pregabalin to Schedule V under the Controlled Substances Act (CSA).ⁱⁱ In the label for Lyrica (pregabalin), reports from clinical studies of subjective effects including euphoria, and withdrawal following discontinuation, are noted in Section 9:

<p>9 DRUG ABUSE AND DEPENDENCE</p> <p>9.1 Controlled Substance</p> <p>LYRICA is a Schedule V controlled substance.</p> <p>LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).</p> <p>9.2 Abuse</p> <p>In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of LYRICA-treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.</p> <p>9.3 Dependence</p> <p>In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see <i>Warnings and Precautions (5.8)</i>], consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.</p>
--

Recent published reports indicate expanding use of gabapentinoids, such as pregabalin and gabapentin, including for off-label pain indications.ⁱⁱⁱ Since pregabalin has a known abuse potential, the long-term effect of this expanded use is unclear, particularly in regards to the concomitant prescribing of gabapentinoids and opioid analgesics. Animal studies have shown the potential for increased risk of respiratory depression and reversal

ⁱ Lyrica label, drugs @ fda: www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

ⁱⁱ Drug Enforcement Administration, DOJ. Schedules of controlled substances: placement of pregabalin into schedule V. Final rule. Federal register 2005;70(144):43633-5.

ⁱⁱⁱ Goodman CW, Brett AS (2017) Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern? *NEJM*, 377, 5: 411-414.

of tolerance due to the additive effect of opioids and pregabalin,^{iv} and respiratory failure and coma have been observed among patients taking pregabalin and other central nervous system (CNS) depressant medications.^v

In 2016, the U.S. Food and Drug Administration (the Agency) required class-wide changes to drug labels describing the serious risks associated with the combined use of opioid analgesics and benzodiazepines. The Agency required boxed warnings for opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concurrently. Risks include extreme sleepiness, respiratory depression, coma and death. A drug safety communication was also issued regarding the use of opioids and other CNS depressant medications, but no labeling changes were made to other CNS depressants medications aside from benzodiazepines.

With enhanced warnings in recent years about opioid analgesics generally, and most recently about the concurrent use of opioid analgesics and benzodiazepines, it is possible that prescribers may channel pain patients, many of whom take opioid analgesics, to gabapentinoid drugs, and the consequences of this potential shift is unknown. In December of 2016, the Agency received a new drug application (NDA) from Pfizer Inc. for an ER pregabalin product (Lyrica controlled-release (CR)). In response to this NDA submission, CSS consulted with the Office of Surveillance and Epidemiology (OSE) requesting data on the abuse or misuse of pregabalin with and without concurrent opioid use to help inform how the marketing of a new pregabalin product with higher dosage units may contribute to the overall public health burden associated with pregabalin abuse and misuse. This review summarizes the current data and literature on pregabalin use and abuse, with and without concurrent opioid use or abuse, and includes recommendations on post-marketing requirements. For comparison, gabapentin was included in all analyses.

1.2 REGULATORY HISTORY AND PHARMACOLOGY

Lyrica (pregabalin) binds with high affinity to the α_2 -delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. The mechanism of action is not entirely known. It is thought that pregabalin increases the density of GABA transporter proteins and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity.

^{iv} Lyndon A, et al. (2017) Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction*, doi:10.1111/add.13843.

^v Lyrica label from drugs@fda:
www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

Lyrica is indicated for the following conditions: neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury, postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, and fibromyalgia.

There are two approved pregabalin formulations, tablet/capsule and solution, approved in 2004 and 2010, respectively (see table below). There are 13 generics under tentative approval in both tablet/capsule and solution formulations.

Approval status	Trade Name (Generic)	Application Number	Applicant	Strengths	Dosage Form/Route
Under review for approval	Lyrica CR (Pregabalin ER)	NDA 209501	Pfizer Inc.	82.5 mg, 165, 330	Tablet Extended-Release/Oral
Approved: 2004	Lyrica (Pregabalin)	NDA 021446	Pfizer Inc.	25 mg, 50, 75, 100, 150, 200, 225, 300	Tablet/capsule
Approved: 2010	Lyrica (Pregabalin)	NDA 022488	Pfizer Inc.	20 mg/ml	Solution

Source: Drugs@FDA.com. Accessed 8/4/2017

2 REVIEW METHODS AND MATERIALS

2.1 DRUG UTILIZATION ANALYSES

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions of the database and their limitations are provided in Appendix A.

In brief, the QuintilesIMS, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for pregabalin and gabapentin from U.S. outpatient retail pharmacies, from 2012 through 2016, annually. The QuintilesIMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for pregabalin and gabapentin from U.S. outpatient retail pharmacies, stratified by patient age (0-17, 18-64, 65 years and older), from 2012 through 2016, annually. Finally, inVentiv Health Research & Insights, LLC., Treatment Answers™ with Pain Panel, a U.S. office-based physician survey database was used to provide information on the occurrences of pregabalin and gabapentin, used alone or concomitantly with other drugs in 2012 and 2016. The term "occurrences" refers to the number of times a drug product has been reported on a physician survey during an office-based patient visit, and may not result in a dispensed prescription. Therefore, these data represent possible concomitant use where the prescriber is aware of or intends to prescribe the patient opioid analgesics and pregabalin or gabapentin.

2.2 AMERICAN ASSOCIATION OF POISON CONTROL CENTER (AAPCC) DATA

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data System (NPDS), which captures data on calls to U.S. poison control centers (PCCs) on a near real-time basis. Currently, AAPCC's 55 PCCs serve individuals across the 50 states as well as U.S. territories including, American Samoa, District of Columbia, Federated States of Micronesia, Guam, Puerto Rico, and the U.S. Virgin Islands. These PCCs receive calls 24 hours per day for exposures to a variety of substances through the "Poison Help Line", and offer medical advice, as needed. All events are documented in the NPDS database. Quality control measures are used to ensure the accuracy and completeness of the data collected. This report contains data from a retrospective analysis of data obtained from the NPDS.

Case records in the database reflect information provided when the public or healthcare professionals call and report an actual or potential exposure to a substance, or request information or educational materials. Exposures do not necessarily represent a poisoning or overdose as the AAPCC does not verify the accuracy of every report made to member centers.

Generic and product codes^{vi} for pharmaceutical preparations with gabapentin (N= (b) (4) generic code and N= (b) (4) product codes) and pregabalin (N= (b) (4) product codes only) were identified using Micromedex® Solutions. Information on human exposure AAPCC calls involving gabapentin and pregabalin from January 1, 2004 through December 31, 2016 were extracted in April 2017. To assess human exposure calls involving gabapentin and pregabalin in combination with opioids and/or heroin, generic and product codes for opioids (N= (b) (4) generic codes) and heroin (N= (b) (4) generic code and N= (b) (4) product codes) were also identified from January 1, 2004 through December 31, 2016, and were subsequently extracted in July 2017. Unique AAPCC case identification numbers were then used to separately match pregabalin and gabapentin human exposure calls to opioid and/or heroin exposure calls. Unique AAPCC case identification numbers were then used to identify human exposure calls involving gabapentin and pregabalin in combination with opioids and/or heroin.

We evaluated trends of pregabalin and gabapentin human exposure calls separately for single-substance exposures (exposure reports involving a single drug product) and for total exposures (involving a single drug product or multiple drug products concurrently) by year.

All exposures classified as "confirmed nonexposure" were excluded. Variable definitions for "medical outcome" and "reason" are noted in Appendix C. Medical outcomes were characterized in total and specifically for calls with a "related" clinical effect. NPDS defined "related" clinical effects as exposures where the following criteria are satisfied: the timing and severity of clinical effects are reasonable for the reported exposure, the

^{vi} LLC THA. Micromedex® Solutions Tox & Drug OProduct Lookup. Secondary Micromedex® Solutions Tox & Drug OProduct Lookup 2017. <http://www.micromedexsolutions.com/micromedex2/librarian>

clinical effect is consistent with the anticipated substance, and the clinical assessment is made by a physician. For multiple drug exposure calls, “related” does not necessarily mean related to one of our drugs of interest. In this context, “related” means the clinical effects were related to one of the substances involved in the exposure, which may or may not be one of our drugs of interest.

2.3 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM – COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)

DEPI searched for adverse drug event (ADE) cases in the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance, or NEISS-CADES, a data resource capturing ADEs that lead to emergency department (ED) visits in a nationally representative sample of hospitals. NEISS-CADES, a joint endeavor of the Centers for Disease Control and Prevention (CDC), the Consumer Product Safety Commission, and FDA, is a database that captures ADE-related ED visits from a sample of 63 hospitals that operate 24-hour EDs in the U.S. ADE cases are identified using clinical records where the physician directly links the use of a drug, or a drug-specific effect, to the condition that resulted in the ED visit. ADE outcomes collected include:

- allergic reactions
- adverse effects
- unintentional ODs
- accidental ingestions
- secondary effects, e.g. choking, or sedative effects precipitating a fall

Note that intentional self-harm, drug therapeutic failures, drug withdrawal, and drug abuse are not currently included in the NEISS-CADES database. National estimates can only be reported if there are ≥ 20 cases on which to base the estimate, the coefficient of variation is $< .30$, and the projected national estimate is $\geq 1,200$ cases.

ED visits involving pregabalin and gabapentin were included from the years 2004-2015, and national projections of ADE-related ED visits associated with those drugs were estimated using hospital-based weights provided by CDC. The generic drug variables were used to identify pregabalin and gabapentin exposures. Non-abuse-related unintentional overdoses (variable name: ADE mechanism), and reports of any opioid in addition to pregabalin, or gabapentin, were also nationally projected over the same time period.

2.4 LITERATURE SEARCH AND REVIEW

In June and August of 2017, DEPI conducted comprehensive literature searches using [PubMed.gov](http://pubmed.gov) to identify published data and studies on pregabalin and gabapentin abuse and misuse, and their consequences (i.e. addiction (substance use disorder), overdose,

and death), with a particular focus on literature discussing concurrent opioid use or abuse. The primary search strategy used was limited to humans and publications in last 10 years:

(**DRUG** = pregabalin, gabapentin, or gabapentinoid)

("DRUG"[MeSH Terms] OR "DRUG"[All Fields]) AND(("substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR "abuse"[All Fields]) OR misuse[All Fields] OR ("drug overdose"[MeSH Terms] OR ("drug"[All Fields] AND "overdose"[All Fields]) OR "drug overdose"[All Fields] OR "overdose"[All Fields]) OR ("death"[MeSH Terms] OR "death"[All Fields]) OR ("behavior, addictive"[MeSH Terms] OR ("behavior"[All Fields] AND "addictive"[All Fields]) OR "addictive behavior"[All Fields] OR "addiction"[All Fields]) OR ("substance-related disorders"[MeSH Terms] OR ("substance-related"[All Fields] AND "disorders"[All Fields]) OR "substance-related disorders"[All Fields] OR ("substance"[All Fields] AND "disorder"[All Fields]) OR "substance use disorder"[All Fields]))

This search strategy identified 136 publications related to pregabalin, 160 related to gabapentin, and four related to gabapentinoids. Although nearly all of the search strategies overlapped with respect to the identified publications, all of the titles and abstracts identified using each search strategy were reviewed. This search was followed up with searches using key words “**DRUG** opioid abuse”, “**DRUG** opioid misuse”, “**DRUG** opioid overdose”, “**DRUG** opioid adverse event”, and “**DRUG** opioid adverse reaction” to ensure no published study related to concurrent pregabalin (or gabapentin) and opioid use or abuse was missed. Most of the identified publications were studies on the safety and effectiveness of off-label gabapentinoid use, commentaries, or case studies/cases series, all of which were excluded. Several pharmacovigilance (spontaneous report) studies from Europe were evaluated and are briefly referenced in this review for completeness, but are not described in detail. In total, only 11 publications were most relevant to this consult and were ultimately reviewed from the searches described above. DEPI also reviewed four additional publications it was aware of through other division projects, media reports, or publications cited within other publications.

These published studies were critically evaluated on their specific methodologies. In this review we provide a summary of the study methods, and a synthesis of its findings. An emphasis was placed on observational studies, but all population-based analyses were included. The studies are broadly categorized into three areas: 1) surveys in high risk populations, 2) surveillance of electronic data (registries, administrative claims, poison centers), and 3) drug-involved mortality investigations.

2.5 GABAPENTINOID COMPARATOR

For comparison, gabapentin was included in all analyses. Gabapentin is structurally similar to pregabalin (both are chemical analogues of GABA), has a similar mechanism of action, has similar clinical indications, and may exhibit similar adverse events, with and without concomitant opioid use.

Gabapentin (Pfizer, Inc.; NDA 020235) was approved by in 1993 indicated as adjunct therapy for partial onset seizures in patients with epilepsy. In 2002, the label was expanded to include an indication for postherpetic neuralgia. Gabapentin is commonly

used off label to treat a number of conditions, including: bipolar disorder, neuropathic pain, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless legs syndrome, trigeminal neuralgia, periodic limb movement disorders of sleep, premenstrual syndrome, migraine, and withdrawal symptoms. Gabapentin is not scheduled under the CSA, but it is available by prescription only and is sold in capsule/tablet and oral solution formulations. There are 32 marketed generic capsule/tablet and oral solution formulations.

The mechanisms by which gabapentin produces its analgesic and antiepileptic effects are not entirely known. Gabapentin is structurally related to the neurotransmitter GABA, but has no effect on GABA binding, uptake, or degradation.^{vii} Gabapentin binds with high-affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels;^{viii} however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

3 REVIEW RESULTS

3.1 DRUG UTILIZATION

The results reported below have been abstracted from Dr. Jennie Wong’s Drug Use Review (DUR), “Utilization Trends for Pregabalin and Gabapentin” (RCM 2017-619). Please see Dr. Wong’s DUR for a complete description of methods and findings.

3.1.1 SETTINGS OF CARE

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to determine the various settings of care in which pregabalin and gabapentin were distributed by the manufacturer in 2016. Sales data capturing the number of bottles/packages sold from manufacturer to all U.S. channels of distribution showed that approximately (b) (4)% of pregabalin was distributed to outpatient retail pharmacies, (b) (4)% to non-retail pharmacies, and (b) (4)% to mail-order/specialty pharmacies. Similarly, approximately (b) (4)% of gabapentin was distributed to outpatient retail pharmacies, (b) (4)% to non-retail pharmacies, and (b) (4)% to mail-order/specialty pharmacies.

Outpatient retail pharmacy utilization patterns were examined for pregabalin and gabapentin. Mail-order/specialty pharmacy and non-retail pharmacy settings data (e.g. hospitals, clinics) were not included in this review.

^{vii} Gabapentin label from drugs@fda:
www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

^{viii} Imani I, Rahimzadeh P (2012) Gabapentinoids: Gabapentin and Pregabalin for Postoperative Pain Management. *Anesthesiology and Pain Medicine*, 2(2):52-53.

3.1.2 PRESCRIPTION DATA

Figure 1 below and Table 1a in Appendix 1 provide the nationally estimated number of prescriptions dispensed for pregabalin and gabapentin from U.S. outpatient retail pharmacies from 2012 through 2016, annually. The total number of prescriptions dispensed for pregabalin increased by $\frac{(b)(4)}{(4)}\%$ from approximately $(b)(4)$ in 2012 to approximately $(b)(4)$ in 2016. In comparison, the number of prescriptions dispensed for gabapentin increased by $\frac{(b)(4)}{(4)}\%$ from approximately $(b)(4)$ in 2012 to $(b)(4)$ in 2016.

Figure 1

Nationally estimated number of dispensed prescriptions for pregabalin and gabapentin^a from U.S. outpatient retail pharmacies



Source: QuintilesIMS, National Prescription Audit (NPA) January 2012 - December 2016 Data extracted May 2017

^a Gabapentin include gabapentin encarbriil (gabapentin prodruq)

3.1.3 PATIENT DATA

Figures 2 and 3 below and Tables 2a in Appendix 1 provide the nationally estimated number of patients who received a prescription for pregabalin and gabapentin, stratified by patient age (0-17, 18-64, 65 years and older) from U.S. outpatient retail pharmacies from 2012 through 2016, annually.

Similar to prescription trends, patient utilization for both drugs increased in the examined time period. The number of patients who received a dispensed prescription for pregabalin increased by $\frac{(b)(4)}{(4)}\%$ from approximately $(b)(4)$ patients in 2012 to approximately $(b)(4)$ patients in 2016. The number of patients who received a dispensed prescription for gabapentin increased by $\frac{(b)(4)}{(4)}\%$ from approximately $(b)(4)$ patients in 2012 to approximately $(b)(4)$ patients in 2016.

The largest proportion of patients who received a dispensed prescription for pregabalin and gabapentin were patients aged 18-64 years, accounting for approximately $(b)(4)\%$ of

the total, followed by patients aged 65 years and older at approximately (b)(4)%^{(b)(4)}. Pediatric patients aged 0-17 years accounted for less than (b)(4)%^{(b)(4)} of total patients for pregabalin and (b)(4)%^{(b)(4)} for gabapentin.

Figure 2

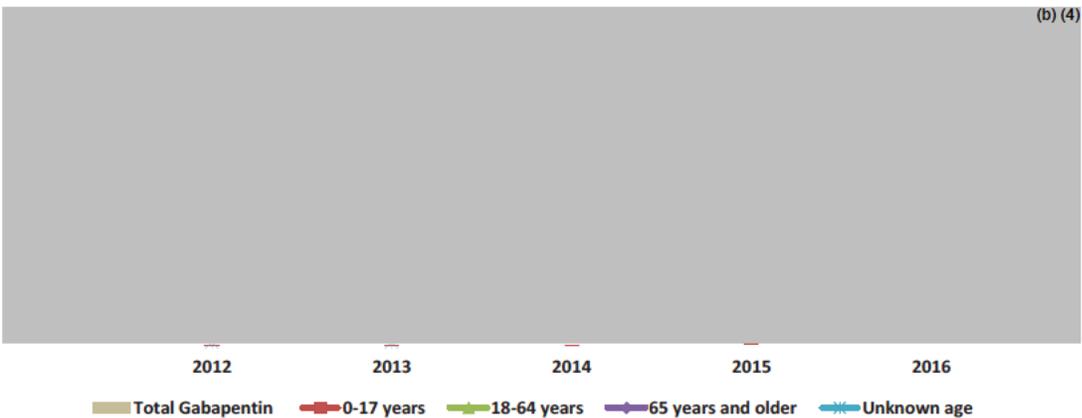
Nationally estimated number of patients* who received a dispensed prescription for pregabalin, stratified by age, from U.S. outpatient retail pharmacies



Source: QuintilesIMS, Total Patient Tracker (TP T) January 2012 - December 2016 Data Extracted May 2017

Figure 3

Nationally estimated number of patients* who received a dispensed prescription for gabapentin, stratified by age, from U.S. outpatient retail pharmacies, 2012-2016



Source: QuintilesIMS, Total Patient Tracker (TP T) January 2012 - December 2016 Data Extracted May 2017

^a Gabapentin include gabapentin encarbnil (gabapentin prodrug)

3.1.4 SURVEY DATA: CONCOMITANCY ANALYSES

Table 1 below provides the estimated number of drug occurrences^{ix} associated with pregabalin, either used alone or with another drug, as reported by U.S. office-based physician survey database for 2016.

A total of (b) (4) drug occurrences for pregabalin were captured in 2016. Of the total, the majority reported pregabalin as being “used alone” accounting for (b) (4)% of the drug occurrences. Approximately (b) (4)% of drug occurrences reported pregabalin to be used along with “oxycodone”. Approximately (b) (4)% of drug occurrences reported pregabalin to be used along with “hydrocodone-acetaminophen” or “oxycodone-acetaminophen”, respectively.

Table 1

Top 10 drug occurrences¹ for pregabalin, used alone or with another drug, reported from U.S. office-based physician survey data, 2016

(b) (4)



¹The term “drug occurrences” to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a “drug occurrence” does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

Note: inVentiv Health Research & Insights, LLC, Treatment AnswersSM cautions that data below 100,000 projected mentions or occurrences may not represent national level trends because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Also, percentages will not add to 100% in share column as some patients may be taking multiple drugs and may be counted in multiple categories, simultaneously.

Table 2 below provides the estimated number of drug occurrences associated with gabapentin, either used alone or with another drug, as reported by U.S. office-based physician survey database for 2016.

^{ix} The term “drug occurrences” to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a “drug occurrence” does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

A total of (b) (4) drug occurrences for gabapentin were captured in 2016. Of the total, the largest percentage reported gabapentin as being “used alone” accounting for (b) (4)% of the drug occurrences. Approximately (b) (4)% of drug occurrences reported gabapentin to be used along with “hydrocodone-acetaminophen”. Approximately (b) (4)% of drug occurrences reported gabapentin to be used along with “cyclobenzaprine” or “oxycodone”, respectively.

Table 2

Top 10 drug occurrences¹ for gabapentin, used alone or with another drug, reported from U.S. office-based physician survey data in 2016

(b) (4)



Source: InVentiv Health Research & Insights, LLC, TreatmentAnswers™ Audit Year 2016 Data extracted July 2017

¹The term “drug occurrences” to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a “drug occurrence” does not necessarily result in a prescription being generated. A “drug occurrence” can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

Note: inVentiv Health Research & Insights, LLC, TreatmentAnswers™ cautions that data below 100,000 projected mentions or occurrences may not represent national level trends because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Also, percentages will not add to 100% in share column as some patients may be taking multiple drugs and may be counted in multiple categories simultaneously.

Using these data, in 2016 pregabalin was reported with the use of opioid analgesics in approximately (b) (4)% of drug occurrences for pregabalin, and gabapentin was reported with the use of opioid analgesics in approximately (b) (4)% of drug occurrences for gabapentin.

When these 2016 data were compared to data from 2012, very little change was observed in the proportion of pregabalin or gabapentin reported with opioid analgesics (data from 2012 are not shown in this review).

3.1.5 DRUG UTILIZATION SUMMARY AND LIMITATIONS

Increasing utilization trends were seen in both the patient and prescription data for pregabalin and gabapentin products. During the examined time period, approximately (b) (4) (b) (4) patients received a dispensed prescription for pregabalin annually. In comparison, the utilization of gabapentin was (b) (4) times higher than pregabalin.

Possible reasons for higher utilization of gabapentin over pregabalin may be attributed to multiple factors, such as, 1) gabapentin is not scheduled as a controlled substance so it may be more accessible to patients compared to pregabalin (Schedule V), 2) gabapentin indicated for use in pediatric patients for adjunct therapy in treatment of epilepsy with partial onset seizures, 3) gabapentin has several off-label uses such as for alcohol withdrawal, fibromyalgia and restless legs syndrome, and 4) gabapentin has a longer marketing history and is available in less expensive generic formulations.^x

Findings from this review should be interpreted in the context of the known limitations of the databases used. We noted that based on sale distribution data, the majority of pregabalin and gabapentin product use occurs in the outpatient retail setting. As a result, we focused our analysis on only the outpatient retail pharmacy settings; thus, these estimates may not apply to other settings of care in which these products are used such as non-federal hospitals, clinics, or mail-order pharmacies.

Office-based physician survey data were used to characterize the concomitant use of pregabalin or gabapentin with other drugs. The term "drug occurrences" refers to the number of times a product has been reported on a survey during an office-based patient visit and may not result in a dispensed prescription; rather, an "occurrence" represents the prescriber's intention to treat. Therefore, these results do not represent a patient-level claims-based analysis of concurrent or overlapping dispensing of opioid analgesics and pregabalin or gabapentin, but do show possible concomitant use where the prescriber is aware of or intends to prescribe the patient opioid analgesics and pregabalin or gabapentin. The data presented are likely an underestimate of the total concurrent use of these drugs, as data on opioid analgesic prescriptions written by a different prescriber, or during a different visit at the same prescriber, may not be reported. In addition, the "drug exposure" estimates may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed. However, these data show that concomitant use of pregabalin or gabapentin with opioids and other central nervous system (CNS) depressants by the same prescriber does occur.

3.2 AAPCC DATA

The results reported below have been abstracted from Dr. Richard Swain's Epidemiology Review, "Memorandum of Pregabalin and Gabapentin Exposure Calls from the National Poison Data System (NPDS)" (RCM 2016-1449). Please see Dr. Swain's review for a complete description of methods and findings.

3.2.1 PREGABALIN AND GABAPENTIN

We identified (b) (4) pregabalin exposure calls between 2005 and 2016, including (b) (4) (b) (4) % single-substance and (b) (4) % multiple-substance calls (Figure 4).

^x Gabapentin: Drug Information. UpToDate®. Lexi-Comp. Wolters Kluwer Health, Inc. Available at: <https://www.uptodate.com/>. Accessed July 10, 2017.

Exposure calls for pregabalin rose sharply for the first few years after FDA approval, with annual calls increasing from (b) (4) in 2005 to (b) (4) in 2008. After 2008, annual multiple-substance calls for pregabalin remained fairly steady, while single-substance and total exposure calls decreased slightly.

We identified (b) (4) gabapentin exposure calls between 2004 and 2016, including (b) (4) (%) single-substance exposures and (b) (4) (%) multiple-substance exposure calls (Figure 5). Exposure calls for gabapentin decreased slightly from 2004 to 2006. Subsequently, the number of calls increased every year for the remainder of the study period, from (b) (4) in 2006 to (b) (4) in 2016. The annual number of exposure calls for pregabalin was less than for gabapentin for each year during the study period. Trends in single-substance, multiple-substance, and total exposure calls over time are displayed in Figures 4 and 5 for pregabalin and gabapentin, respectively.

Figure 4. Total annual exposure calls for pregabalin, 2004-2016

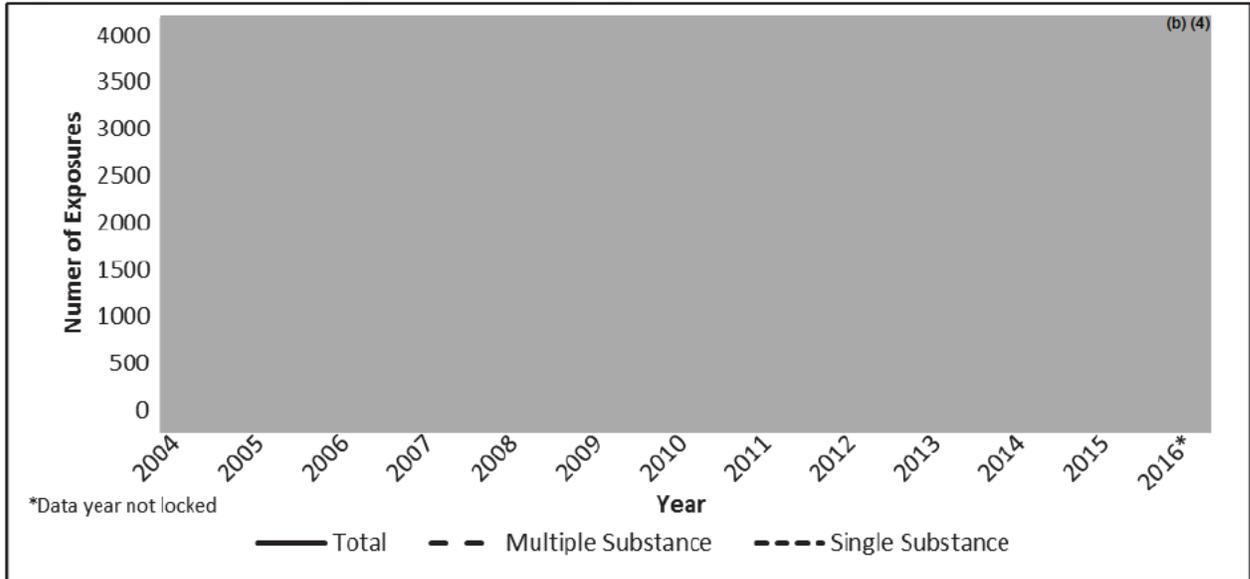
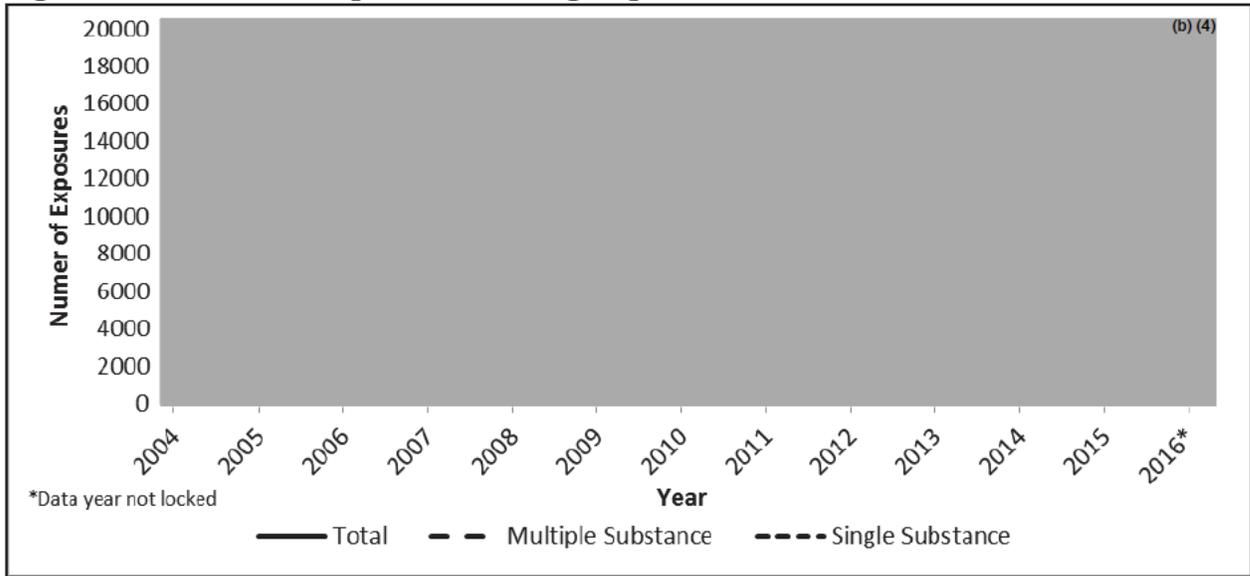
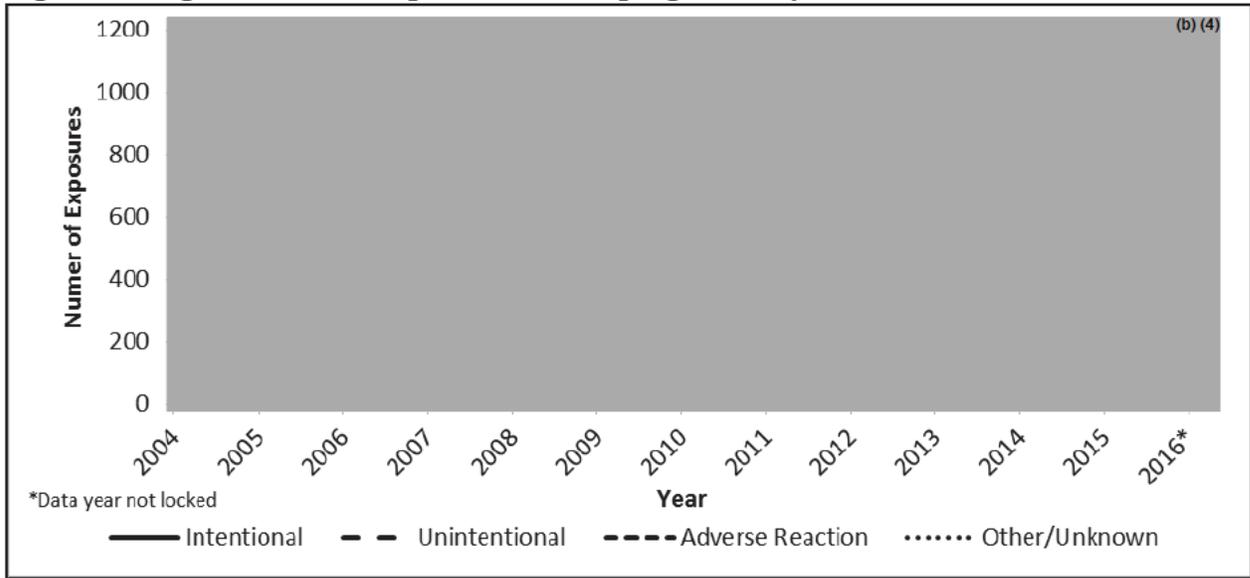


Figure 5. Total annual exposure calls for gabapentin, 2004-2016



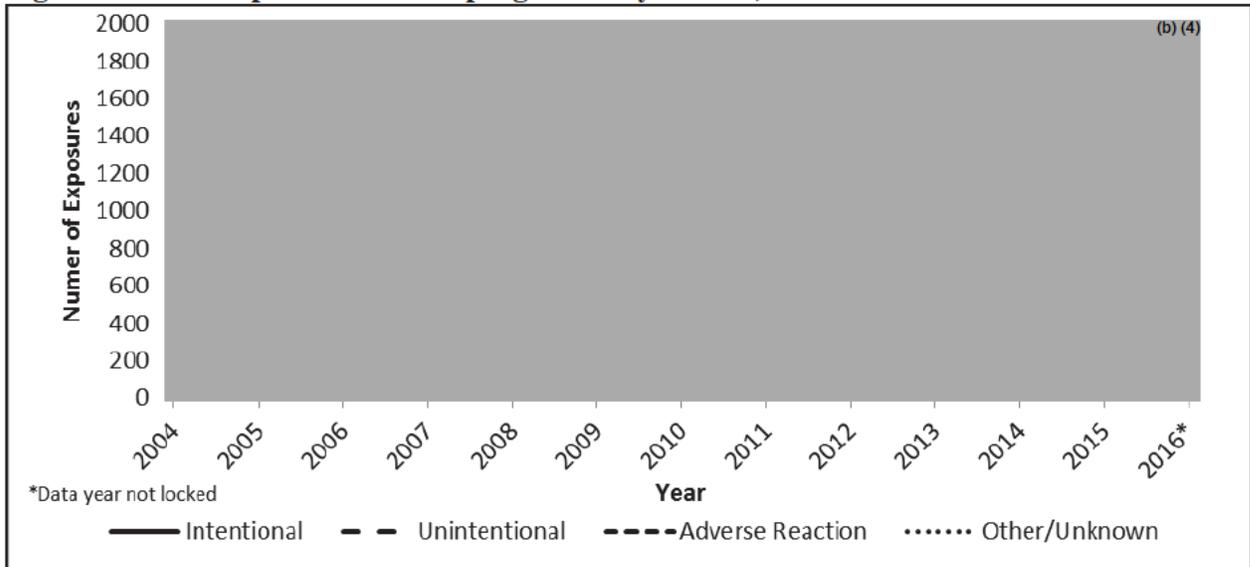
During the study period, single-substance exposures for pregabalin were classified as intentional (n= (b) (4) %), unintentional (n= (b) (4) %), adverse reaction (n=1,011, (b) (4) %), and other/unknown (n= (b) (4) %). Unintentional exposures accounted for the majority ((b) (4) %) of exposure calls from 2005 to 2008, more than doubling intentional exposures for each of those years. From 2008 to 2016, unintentional exposures showed a decreasing trend from (b) (4) calls in 2008, to (b) (4) in 2016, while the number of intentional exposure calls remained relatively steady. By the end of the study period, intentional exposure calls (n= (b) (4) in 2016) nearly equaled unintentional (n= (b) (4) in 2016) exposure calls. Calls reporting an adverse reaction to a single-substance pregabalin exposure peaked in number and proportion (n= (b) (4); (b) (4) %) in 2008, steadily declining thereafter (to n= (b) (4) % in 2016). Reasons for single-substance pregabalin exposures are shown in Figure 6.

Figure 6: Single-substance exposure calls for pregabalin by reason, 2004-2016



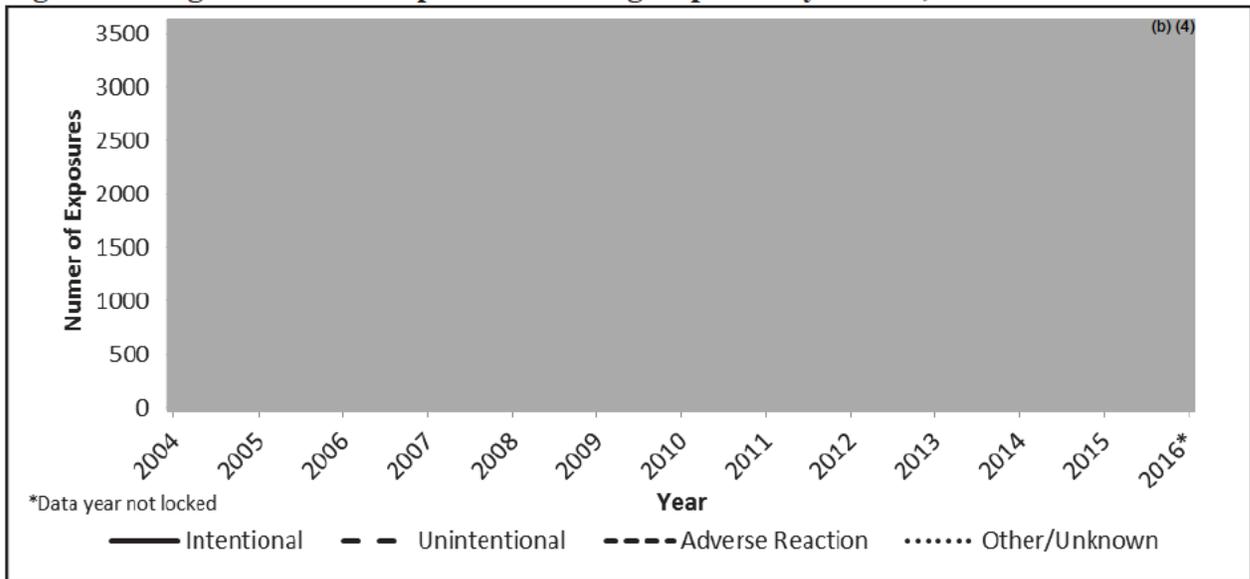
Total pregabalin exposure calls were reported as intentional (n= (b)(4) %), unintentional (n= (b)(4) %), adverse reaction (n= (b)(4) %), and other/unknown (n= (b)(4) %). Trends for unintentional, adverse reaction and other/unknown reasons for exposure among total pregabalin exposure calls were similar to single-substance exposures, peaking in 2008 and declining slightly through the end of the study period. Intentional calls accounted for a larger proportion of total exposure calls, compared to single-substance calls, accounting for (b)(4) % of calls in 2016. The annual number of intentional exposure calls increased in each of the last four years of the study period. Reasons for total annual exposure calls for pregabalin are shown in Figure 7.

Figure 7: Total exposure calls for pregabalin by reason, 2004-2016



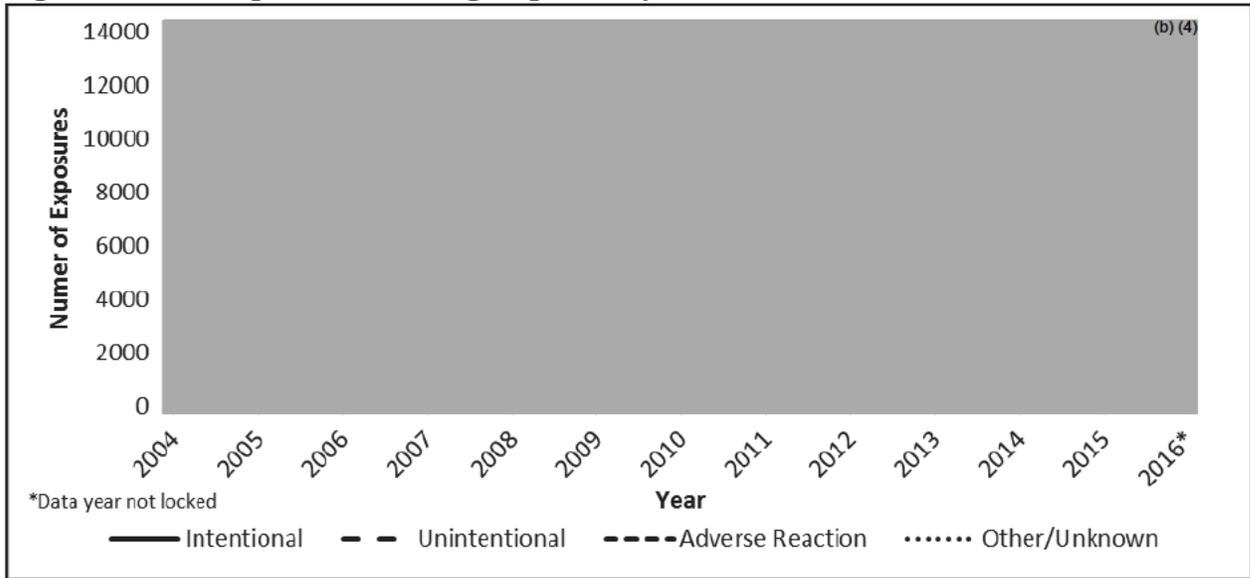
Reasons for single-substance exposures for gabapentin followed a similar rank order as those for pregabalin. During the study period, single-substance gabapentin exposure calls were classified as intentional (n= (b) (4) %), unintentional (n= (b) (4) %), adverse reaction (n= (b) (4) %), and other/unknown (n= (b) (4) %). As with pregabalin, unintentional gabapentin calls accounted for the majority of single-substance exposures for most of the study period, with the gap between unintentional and intentional narrowing during later years. However, unlike pregabalin, intentional single-substance exposures outnumbered unintentional exposures in 2015 and 2016. Reasons for single-substance exposure calls for gabapentin from 2004 to 2016 are shown in Figure 8.

Figure 8: Single-substance exposure calls for gabapentin by reason, 2004-2016



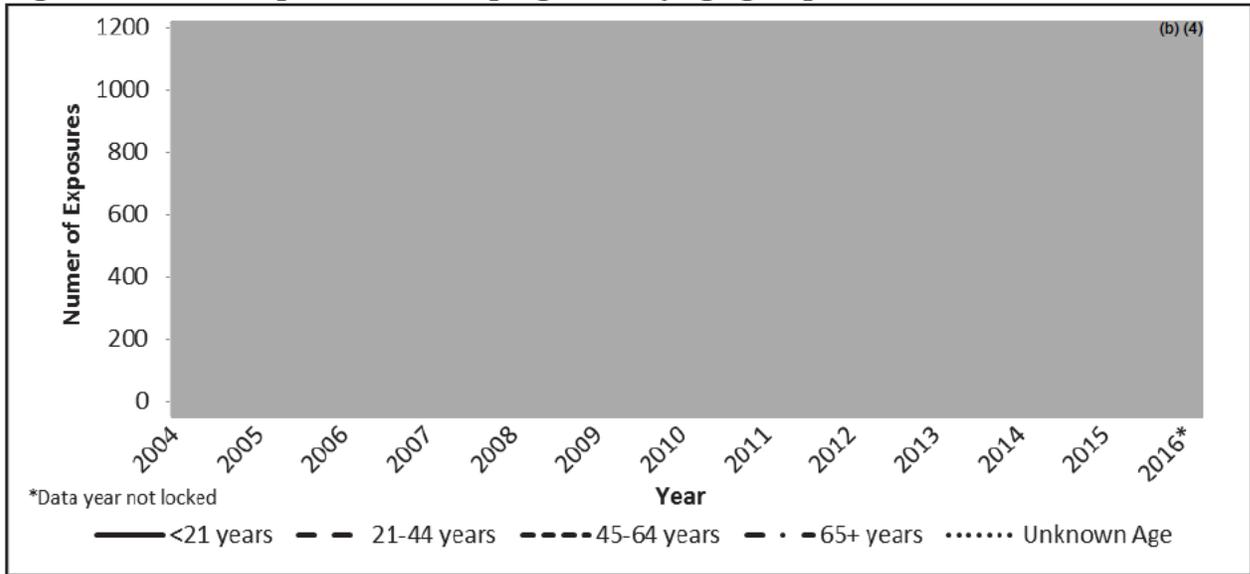
Total exposure calls for gabapentin were recorded as intentional (n= (b) (4) %), unintentional (n= (b) (4) %), adverse reaction (n= (b) (4) %), and other/unknown (n= (b) (4) %). As with total pregabalin exposures, intentional and unintentional calls accounted for similar proportions of total calls early in the study period, with increasing number and proportion of intentional calls in later years. Intentional exposures accounted for (b) (4) % calls in 2006 and (b) (4) % calls in 2016. However, the number and proportion of intentional gabapentin exposure calls increased more sharply than intentional pregabalin calls, and while unintentional pregabalin calls decreased after peaking in 2008, unintentional gabapentin calls increased every year after 2006. Total annual gabapentin exposure calls by reason are shown in Figure 9.

Figure 9: Total exposure calls for gabapentin by reason, 2004-2016



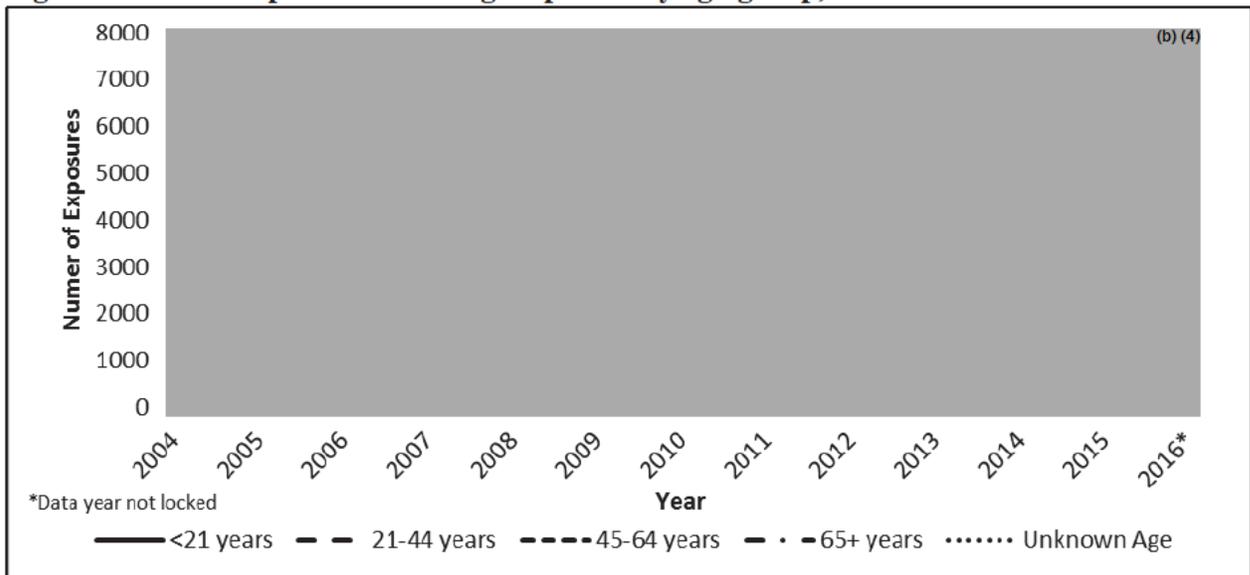
During the study period, age-groups for total exposure calls for pregabalin were recorded as less than 21 years (n= (b) (4) %), 21 to 44 years (n= (b) (4) %), 45 to 64 years (n= (b) (4) %), 65 years and older ((b) (4) %), and unknown age (n= (b) (4) %). The mean ((b) (4) years) and median (40 years) ages for total pregabalin exposure calls were slightly older compared to single-substance exposures (data not shown; see Swain’s Epidemiology Review: Memorandum of Pregabalin and Gabapentin Exposure Calls from the National Poison Data System). Age-group specific trends among total pregabalin exposures were very similar to those among single-substance exposures, with calls from the 21 years and older age-groups fairly steady beginning in 2008 while the total number of exposure calls pertaining to persons younger than 21 years declined. The younger than 21 year age-group consisted of a smaller proportion of total calls ((b) (4) %) compared to single-substance ((b) (4) %) exposures. Annual total pregabalin exposure calls by age-group are shown in Figure 10.

Figure 10: Total exposure calls for pregabalin by age group, 2004-2016



Age groups for total gabapentin exposure calls were reported as less than 21 years ($n = (b)(4)$, .6%), 21 to 44 years ($n = (b)(4)$), 45 to 64 years ($n = (b)(4)$), 65 years and older ($n = (b)(4)$), and unknown ($n = (b)(4)$), and the mean (median) age was $(b)(4)$ (40) years. Similar to single-substance gabapentin exposures (data not shown; see Swain’s Epidemiology Review: Memorandum of Pregabalin and Gabapentin Exposure Calls from the National Poison Data System), and in contrast to total pregabalin exposures, total gabapentin exposures increased for each age-group every year after 2006. Total gabapentin exposure calls tended to involve slightly older persons, with the less than 21 year age-group accounting for a smaller proportion of exposures compared to single-substance exposure calls. Annual total gabapentin exposure calls by age-group are shown in Figure 11.

Figure 11: Total exposure calls for gabapentin by age group, 2004-2016



Medical outcomes associated with pregabalin and gabapentin single-substance and total exposure calls with “related” clinical effects (“moderate effect”, “major effect” and “death” only) from 2004 through 2016 are displayed in Table 3. Trends and patterns for “related” medical outcomes were similar to those described for all (including “unrelated”) medical outcomes, though they were slightly fewer in number due to outcomes with non-related clinical effects being excluded (*See Table 4a in Appendix D for all medical outcomes*).

The proportion of pregabalin single-substance and total exposure calls associated with a moderate, major, or death outcome was (n= (b) (4) %) and (n= (b) (4) %), respectively. Opioid use was recorded for (b) (4) (n= (b) (4) %) of pregabalin exposure calls that resulted in death. The proportions of gabapentin single-substance (n= (b) (4) %) and total exposure (n= (b) (4) %) calls associated with a moderate, major, or death outcome were slightly lower for gabapentin compared to pregabalin. Opioid use was recorded for (b) (4) (n= (b) (4) %) of gabapentin exposure calls that resulted in death.

Table 3: Frequencies for pregabalin and gabapentin Exposures with Medical Outcomes Related to Exposure

Drug Year	Medical Outcome							
	Single Substance Exposure Calls				Total Exposure Calls			
	Moderate	Major	Death	Total	Moderate	Major	Death	Total
Pregabalin								(b) (4)
2005								(b) (4)
2006								
2007								
2008								
2009								
2010								
2011								
2012								
2013								
2014								
2015								
2016*								
Gabapentin								
2004								
2005								
2006								
2007								
2008								
2009								
2010								
2011								
2012								
2013								
2014								
2015								
2016*								

*Data year not locked

3.2.2 EXPOSURE CALLS WITH OPIOIDS AND/OR HEROIN

The proportion of total exposure calls including an opioid was slightly higher for pregabalin (n= (b) (4) %) compared to gabapentin (n= (b) (4) %). During the last several years of the study period, the number of opioid-related calls remained fairly stable for pregabalin exposure and rose slightly for gabapentin; however, the proportion of total calls containing an opioid declined for both drugs during this time. The proportion of exposure calls including opioid exposure peaked for pregabalin (n= (b) (4) %) in 2011 and for gabapentin (n= (b) (4) %) in 2012, and steadily decreased thereafter. The frequency of opioid exposure among total pregabalin and gabapentin exposure calls is shown in Figures 12 and 13, respectively.

Figure 12: Annual exposure calls for pregabalin by opioid status, 2004-2016

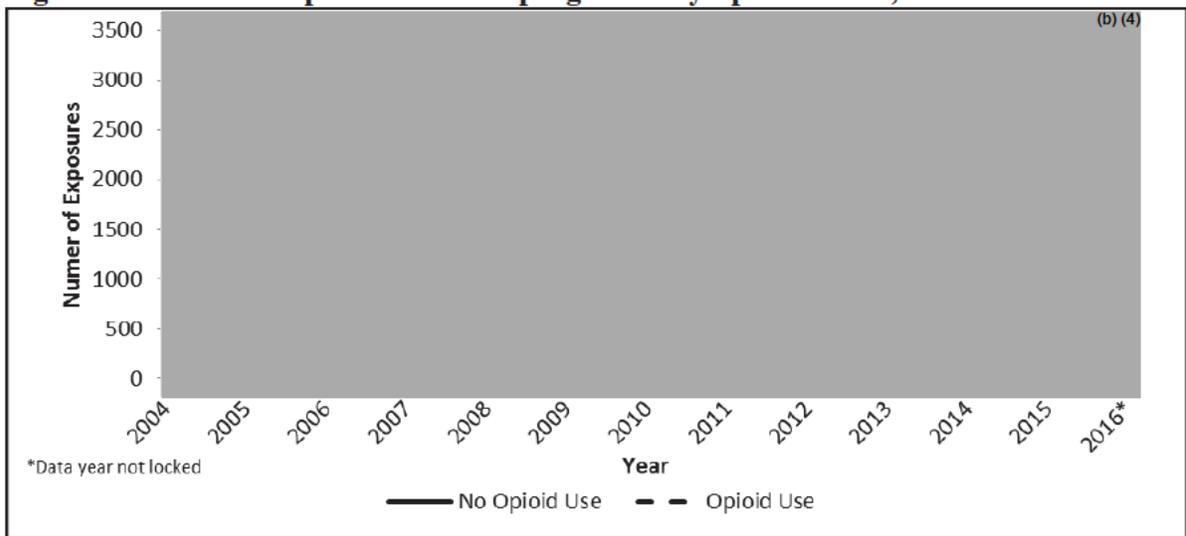
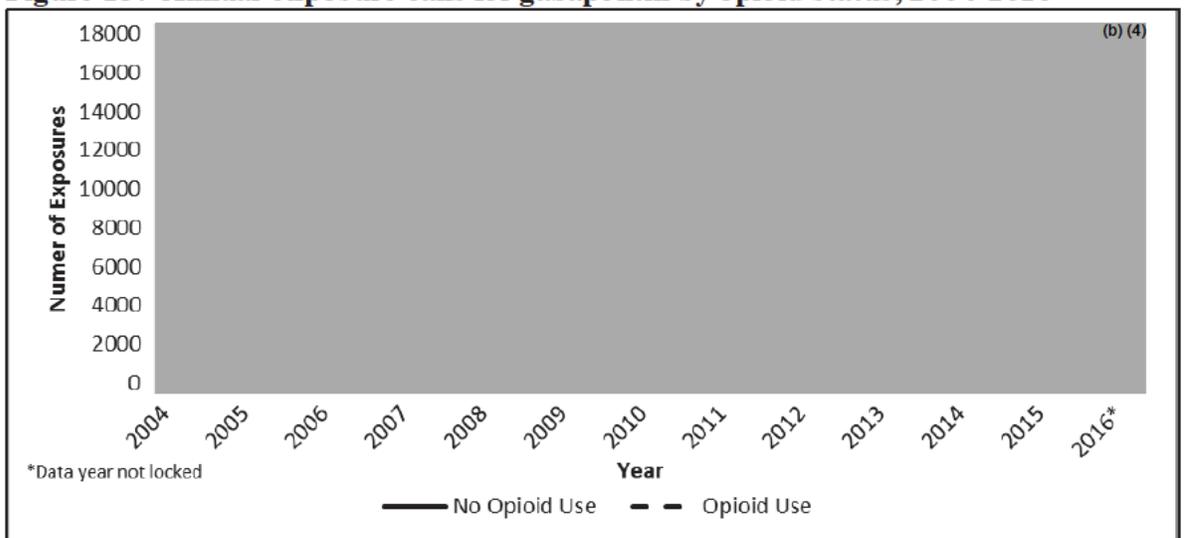


Figure 13: Annual exposure calls for gabapentin by opioid status, 2004-2016



During the study period, the proportion of total exposure calls including heroin was lower for pregabalin ((b) (4)%) compared to gabapentin ((b) (4)%). Though heroin exposure was rare, we observed an increasing trend toward the end of the study period. For example, from 2009 to 2010, we identified ((b) (4)%) heroin exposure calls among pregabalin exposure calls and ((b) (4)%) among gabapentin exposures. From 2015 to 2016, the number of heroin exposures calls increased to ((b) (4)%) among total pregabalin exposure calls and ((b) (4)%) among total gabapentin exposure calls.

3.2.3 NORMALIZED EXPOSURE CALL RATES

Using the total prescription dispensed data from Appendix B, and annual total AAPCC calls, rates were normalized by year using prescriptions dispensed and total call volume.

Pregabalin single-substance and total exposure calls per 100,000 prescriptions dispensed remained relatively consistent throughout the study period (See Table 4 and Figure 14 below). Pregabalin single-substance and total exposure calls per 100,000 AAPCC exposure calls rose slightly throughout the study period, likely a reflection of decreased call volume to PCCs and an increase in calls mentioning pregabalin. Similar rates and trends were seen for gabapentin per 100,000 prescriptions dispensed as were seen for pregabalin, but rates per 100,000 AAPCC exposure calls were much higher for gabapentin compared to pregabalin (See Table 4 below).

Table 4: Number and rate of pregabalin and gabapentin single and total exposures

	Study Year				
	2012	2013	2014	2015	2016
Pregabalin	(b) (4)				
Single Substance Exposures (n)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					
Total Exposures (N)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					
Gabapentin					
Single Substance Exposures (n)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					
Total Exposures (N)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					

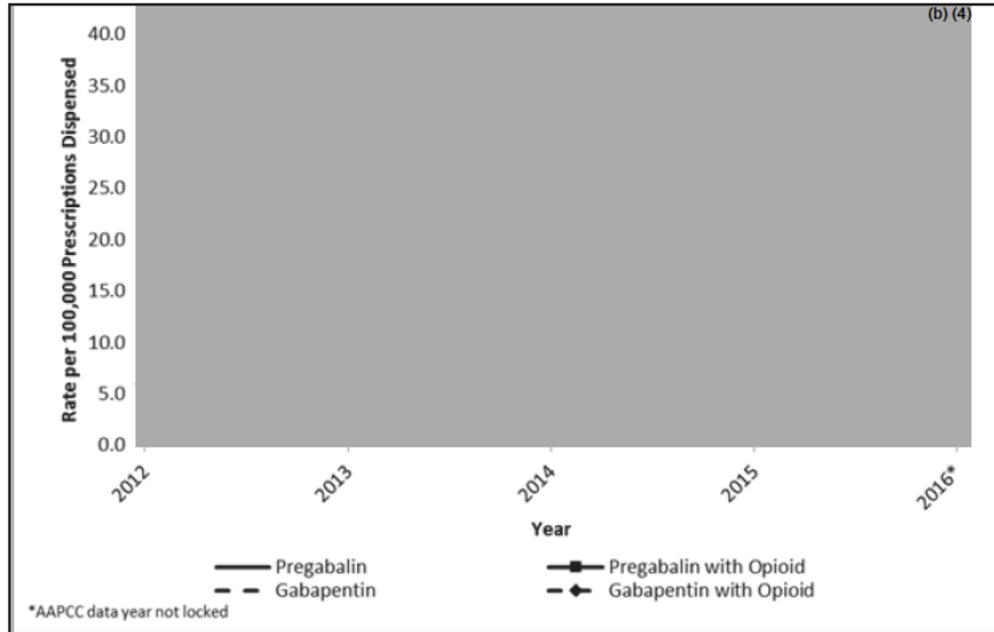
Pregabalin exposure calls with an opioid per 100,000 pregabalin prescriptions dispensed and per 100,000 AAPCC exposure calls also remained relatively consistent throughout the study period (See Table 5 below). Similar rates were seen for gabapentin with an opioid per 100,000 gabapentin prescriptions dispensed as were seen for pregabalin (See Table 5 and Figure 14 below).

Table 5: Number and rate of pregabalin + opioid and gabapentin + opioid exposures

	Study Year				
	2012	2013	2014	2015	2016
Pregabalin Exposure Calls (N)	(b) (4)				
Opioid Exposures (n)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					
Gabapentin Exposure Calls (N)					
Opioid Exposures (n)					
Rate per 100,000 Rx Dispensed					
Rate per 100,000 AAPCC Exposure Calls					

NOTE: prescriptions dispensed refers to either pregabalin or gabapentin dispensed, not concomitant or overlapping dispensing of pregabalin or gabapentin and an opioid

Figure 14: Rates of AAPCC calls per 100,000 prescriptions dispensed related to pregabalin and gabapentin exposures, 2012-2016



3.2.4 AAPCC DATA SUMMARY AND LIMITATIONS

Overall, we identified (b) (4) total pregabalin exposure calls between 2005 and 2016, including (b) (4) single-substance exposure calls. Pregabalin exposure calls rose sharply after market approval in 2005, and remained fairly steady after 2008. We identified (b) (4) total gabapentin exposure calls between 2004 and 2016, including (b) (4) single-substance exposures calls. Gabapentin exposure calls decreased from 2004 to 2006, and increased every year from 2007 to 2016. The proportion of pregabalin exposure calls related to intentional exposures was lower than gabapentin, but higher for related moderate, major, or death medical outcomes, and exposure calls indicating concurrent opioid exposure. Pregabalin and gabapentin total exposure rates per 100,000 prescriptions

dispensed were similar and remained relatively consistent from 2012 to 2016. The rate of concurrent pregabalin and opioid exposure calls per 100,000 pregabalin prescriptions dispensed was slightly higher compared to the corresponding rate for gabapentin.

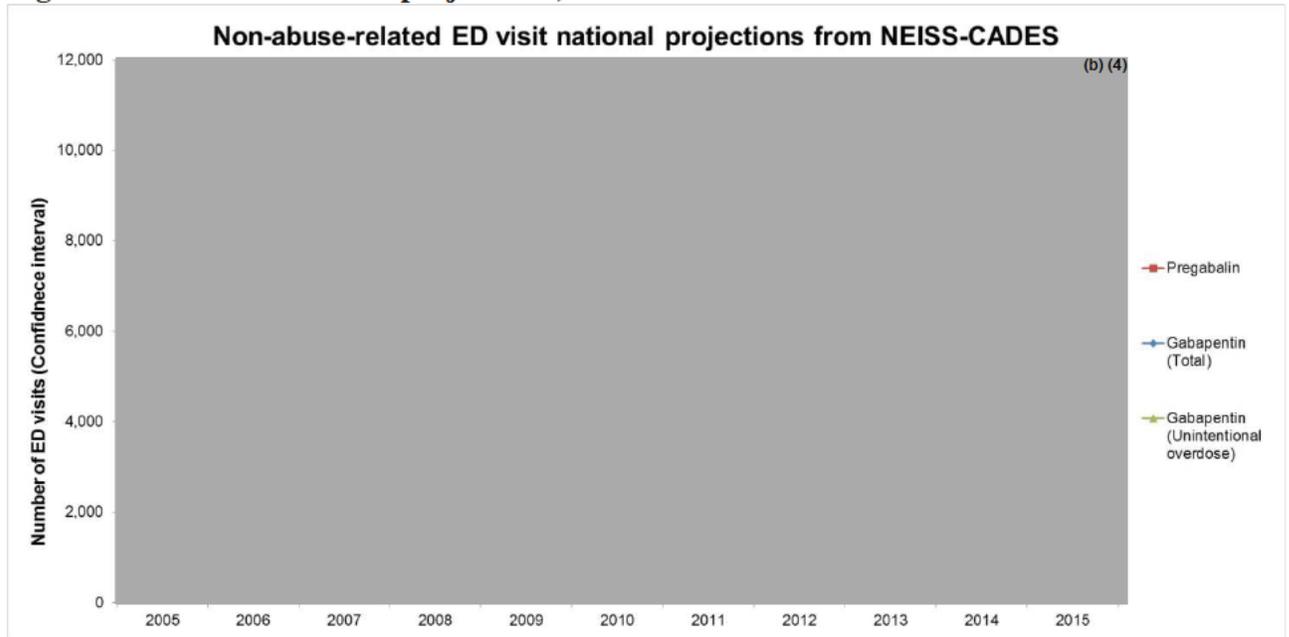
This analysis has several limitations that must be taken into consideration when interpreting the results. Trends and patterns in reasons, age distribution, and medical outcome for single-substance versus total exposure calls for pregabalin and gabapentin were noticeably different, indicating that total exposure patterns were largely influenced by multiple-substance exposures, which are not shown. Exploratory data analyses showed that some opioid and heroin exposures were not included in the analyses. The AAPCC categorizes drugs by “product code” and “generic code”; however, some generic codes include categories for miscellaneous, often combination, products. Consequently, opioid and heroin exposure calls were slightly undercounted.

NPDS poison center call data have limitations, and referenced AAPCC data should not be construed to represent the complete incidence of national exposures to any substance(s). These data only capture abuse events if the exposure resulted in a call to a PCC. Poison control center call data rely on information shared by patients and healthcare personnel, and most substance classification is based on self-report alone and does not involve any laboratory confirmation. Follow-up and medical outcome information are not available for all calls. It is possible that changes in PCC call rates in part reflect changes in public and professional awareness of the risks associated with specific drugs. Call rates may also be influenced by general changes in use of PCCs over time. Awareness of the abuse potential of specific drugs among PCC personnel could increase the likelihood of an exposure being coded as intentional abuse.

3.3 NEISS-CADES DATA

National projections of the total number of non-abuse-related ED visits associated with pregabalin and gabapentin were estimated from 2005-2015 (See Figure 15 below and Table 5a in Appendix E). Rates were also estimated for non-abuse-related unintentional overdose associated gabapentin exposure. From 2009 onward, the total number non-abuse-related ED visits for gabapentin rose from (b) (4) (Confidence interval (CI): (b) (4)) in 2009 to (b) (4) in 2015, with the exception of 2013. Non-abuse-related unintentional overdose associated gabapentin exposure also rose from 2010 to 2015 from (b) (4). The total number non-abuse-related ED visits for pregabalin rose slightly from 2006 (b) (4) to 2015 (b) (4), but hovered around (b) (4) per year. Annual national estimates for the number of ED visits related to pregabalin and opioid use, or unintentional overdose associated pregabalin, could not be computed because there were not enough observed cases from which to make national projections. Similarly, annual estimates for ED visits related to gabapentin and opioid use could not be computed.

Figure 15: ED visit national projections, 2005-2015



NOTE: A missing data point(s) on figure means that a national estimate(s) could not be computed.

Cumulative national estimates for 2004-2015 were calculated for several exposure categories (see Table 6 below):

- non-abuse-related unintentional overdose associated with pregabalin exposure,
- non-abuse-related ED visits associated with gabapentin and an opioid analgesic, and
- non-abuse-related ED visits associated with gabapentin and an opioid analgesic where unintentional overdose was noted in the record.

ED visits related to pregabalin and opioid use could not be computed for this time period because there were not enough observed cases from which to make national projections.

Table 6: ED visit national projections, 2004-2015

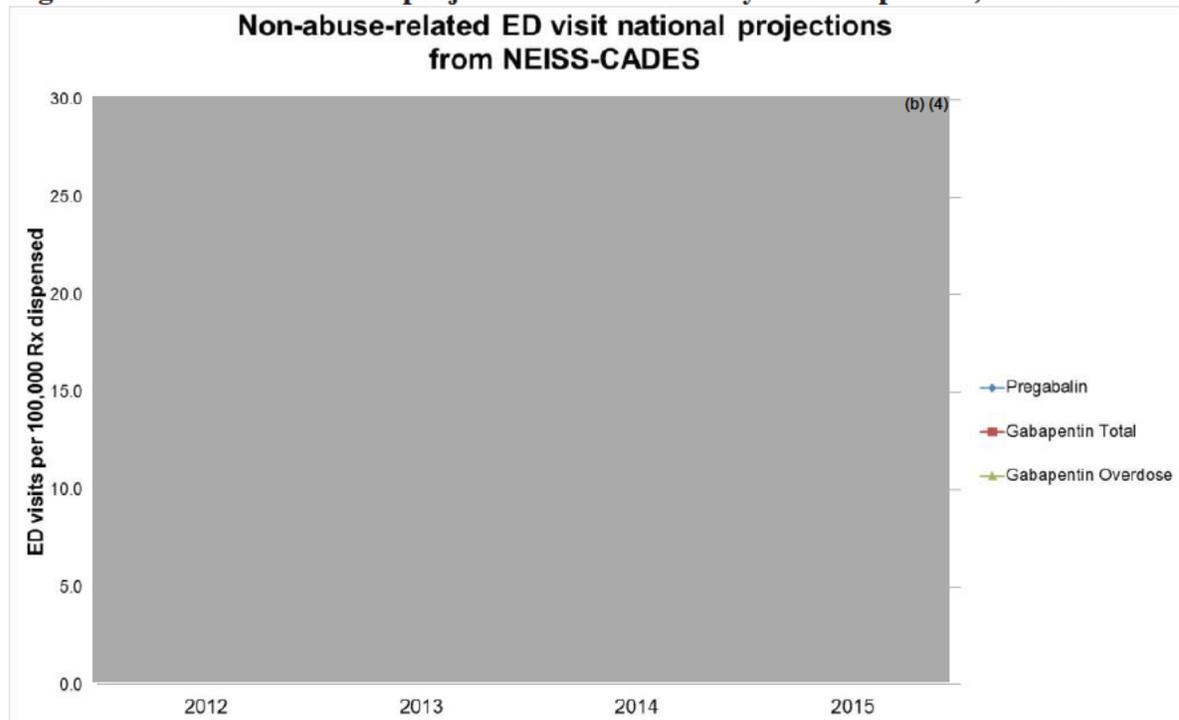
	National estimate ED visits cumulative 2004-2015 (Confidence interval)	
Pregabalin (Unintentional overdose only)		(b) (4)
Gabapentin (w/ opioid)		
Gabapentin (w/ opioid & unintentional overdose only)		

Using the total prescriptions dispensed data from Appendix B, rates were normalized from 2012-2016 (see Figure 16 below).

While the number of non-abuse-related ED visits per 100,000 prescriptions dispensed decreased from 2012 to 2015 for both total visits associated with gabapentin, and those where an unintentional overdose was noted, pregabalin shows a large drop in non-abuse-

related ED visits per 100,000 prescriptions dispensed from 2012 to 2013 (similar to gabapentin) followed by a large increase from 2013 to 2015. The increase in pregabalin non-abuse-related ED visits per 100,000 prescriptions is likely due to increases in ED visits since pregabalin utilization remained steady during that time period.

Figure 16: ED visit national projections normalized by Rx's dispensed, 2012-2015



3.3.1 NEISS-CADES DATA SUMMARY AND LIMITATIONS

Overall, there were large increases in the estimates of non-abuse-related ED visits for gabapentin from 2005- 2015, but that may be due to commensurate increases in gabapentin utilization over that time as evidenced by the normalized rates in the last 4 years of that period. For pregabalin, there were slight increases in ED visit estimates from 2012-2015 with stable prescriptions dispensed over that period resulting in increases in normalized rates (per 100,000 prescriptions dispensed).

There are several limitations to note for NEISS-CADES data, and this analysis, specifically. NEISS-CADES data have a relatively low sensitivity. This means that the national estimates are likely lower than the true number of ED visits in U.S. for a given time period. Only two drugs can be implicated in each case meaning that any non-abuse-related ED visit that involved more than two drugs would be missing information on the other involved drugs. Emergency department visits related to abuse-related exposures are currently systematically excluded from NEISS-CADES data; therefore, these estimates are not exhaustive of all potential drug-related ED visits. This is important in the context of this review as pregabalin has a known abuse potential. For that reason, these estimates are used more for understanding larger post-market adverse drug event trends for the

gabapentinoid drugs. Finally, many annual and cumulative (2004-2015) national projections could not be calculated due a small number observed cases from which to make the projection.

3.4 LITERATURE REVIEW

The studies of primary interest are broadly categorized into three areas: 1) surveys in high risk populations (3.4.1), 2) surveillance of electronic data (registries, administrative claims, poison centers) (3.4.2), and 3) drug-involved mortality investigations (3.4.3).

3.4.1 SURVEYS IN HIGH RISK POPULATIONS

There have been several recent investigations where opioid dependent individuals have been surveyed on their drug taking preferences and behaviors. In a study by Baird et al., [1] a questionnaire-based survey was conducted over a 3-month period in 2011 in six substance abuse clinics in Scotland assessing for gabapentinoid abuse. Of the 129 who completed the survey, 25 (19%) reported taking non-prescribed gabapentin and 4 (3%) non-prescribed pregabalin. Several others were taking gabapentin (n=9) and pregabalin (n=2) prescribed to them legitimately. Of those taking non-prescribed gabapentinoids, all were on prescribed methadone for opioid dependency, 22 (76%) said they used gabapentinoids to become intoxicated, and 11 (38%) said they used gabapentinoids to potentiate the euphoric effect of the methadone. Wilens et al [2] prospectively assessed consecutive admissions to a public detoxification program in Massachusetts in 2013 using a self-report questionnaire to capture the use of specific psychotropic medications. Among all surveyed admissions for both alcohol and opioid detox (n=196), 20% reported receiving a prescription for gabapentin and 2% for pregabalin, and among those 36% and 50% reported using higher than prescribed doses for gabapentin and pregabalin, respectively. Another 11% and 5% of the surveyed admissions reported using gabapentin and pregabalin without a legitimate prescription, respectively. Similar percentages were observed when restricting to only those admitted for detox from opioids only.

Dahlman et al [3] interviewed a randomly-selected group of patients receiving medication assisted treatment (MAT) at two MAT clinics in Sweden between October 2014 and December 2015 (n=73) about their motivations for use of prescription drugs, and acquisition and administration of prescription drugs. The study was based on self-reports from structured interviews. The interviews were performed using a survey tool based on two questionnaires developed at RTI International for the purpose of investigating nonmedical use of promethazine and general nonmedical use of prescription drugs. Thirty-six percent of the sample (n=26) reported using pregabalin in their lifetime, 21% (n=15) reported non-medical use of pregabalin, and 23% (n=17) reporting using pregabalin in combination with methadone, buprenorphine, or heroin. Of those reporting using pregabalin in combination with methadone, buprenorphine, or heroin, 65% (n=11) reported using pregabalin to potentiate the euphoric effects of the opioids. Of those ever using pregabalin, illicit acquisition of pregabalin was reported by 46% (n=12) of participants. Gender, age, and MAT type were not associated with non-medical use of pregabalin in this population; other variables were not assessed.

In a small study of heroin users (n=30) by Lyndon et al [4], recruited through selected sampling (based on gender and duration of heroin use), qualitative interviews were conducted assessing gabapentinoid use, and perception of gabapentinoids in the community. Twenty-one participants had experience using gabapentinoids, and 3 used them daily. Participants reporting use of pregabalin stated that the combination of heroin and pregabalin enhanced the subjective effects, but that the risk of overdose was greater. Some participants noted that pregabalin may actually reduce heroin use when used in certain situations, but the reasons were unclear. Smith et al. [5] assessed a prescription drug abusing cohort not currently in treatment (n=503) in rural Kentucky.^{xi} Fifteen percent (n=75) of participants reported using gabapentin “to get high” in the last 6 months which is a 165% increase from the year prior, a 2,950% increase since 2008. It is unclear whether the same participants were interviewed in each calendar year. Participants reported using gabapentin an average of 25 of the past 30 days, and those reporting gabapentin use were more likely than nonusers to abuse immediate-release oxycodone, buprenorphine, and benzodiazepines in the prior 30 days “to get high.” The two major sources of gabapentin were physicians (52%) and drug dealers (36%), and street cost were reported to be less than \$1.00 per pill. Several participants reported using dosages outside the range of standard medical care.

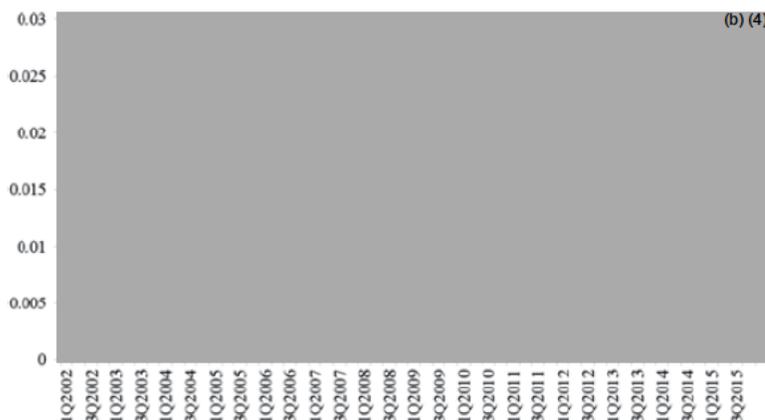
Bastiaens et al. [6] evaluated gabapentin misuse in a dually-diagnosed correctional population, and evaluated if misuse was associated with opioid use disorder (OUD). Two-hundred and fifty former inmates living in a correctional community center who were administered a psychiatric evaluation were also surveyed on their non-medical use of opioids and gabapentin. Fifty-eight percent had an opioid use disorder, and 16% percent reported having misused gabapentin in the past. Of patients with an OUD (n =145), 26% reported nonmedical use of gabapentin while only 4% of patients without an OUD (n=105) reported nonmedical use of gabapentin (p<0.001).

Law enforcement have also been surveyed (Buttram et al. [7]) as part of the drug diversion program of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System, a national prescription drug surveillance system. The Drug Diversion Program includes a voluntary quarterly survey of a national convenience sample of law enforcement and regulatory agencies who conduct in drug diversion investigations in 41 states (the exceptions include Hawaii, Indiana, Kansas, New Jersey, New York, Texas, Washington, West Virginia, and Wyoming). Using a standardized quarterly survey, participants record the number of new cases investigated by the agency during past 3 months, and the specific drugs involved in each case. The survey does not specifically ask about gabapentin, but there is a “write-in” section where agencies can note additional diverted drugs. A total of (b) (4) cases of gabapentin diversion were reported to RADARS in 2016. This is likely a significant underreporting of cases nationally given that information on gabapentin was only collected through the “write in” section of the survey, and that not all states have agencies that report to RADARS. The rates have steadily increased (p<0.001) from (b) (4) cases in the first 2 quarters of 2002 to a high of

^{xi} The date of study was not given; this study was submitted as a letter to the editor. The likely year was approximately 2013.

(b) (4) cases (per 100 000 population) in the fourth quarter of 2015 (See figure below). Seventy-three drug diversion program agencies responded to the optional brief questionnaire noting that gabapentin demand is related to the misuse/abuse of opioids, and that agencies have seen an increase in gabapentin diversion in their jurisdictions. The street price in Michigan was noted to be \$10 per pill.

Figure from Buttram: Rates of gabapentin diversion per 100,000 population, 2002-2015*



*based on law enforcement reports

Kapil et al [8] conducted an online survey of prescription drug misuse partnered with a global market research company, GMI, which has an established global consumer panel of millions of individuals. Invitations to participate were sent by GMI to existing market research panel members in the UK only, between the ages of 16 and 59 years. It is unclear whether this population was of high risk for prescription drug abuse. Of the 1,500 who participated, (b) (4) reported misusing gabapentin, and (b) (4) reported misusing pregabalin.

3.4.1.1 SURVEY LITERATURE SUMMARY AND LIMITATIONS

Data from these survey-based investigations suggest that gabapentinoid misuse and abuse is particularly problematic among those who abuse prescription opioids and heroin, and those in treatment for substance abuse, including MAT. Both the Buttram et al and Smith et al. studies appear to show increases in recent years in the reporting of diversion and misuse/abuse of gabapentin, respectively. It also appears that the concurrent misuse of gabapentinoids and opioids is primarily to enhance the effect of the opioid.

All of these studies have similar limitations. They are small, cross-sectional studies in highly selected populations with unknown representativeness and generalizability. No study corroborated self-report with toxicological analysis. The Buttram et al. study used a convenience sample of law enforcement and regulatory agencies that also may not be representative of all law enforcement and regulatory agencies, and under-reporting was likely. It is also unclear whether diversion is an appropriate surrogate signal of misuse or abuse. The Smith et al. study used respondent driven sampling in the generation of their cohort, but it is unclear whether the same cohort of prescription drug abusers is followed prospectively, or if data are based on cross-sectional, one-time surveys of different participants over time.

3.4.2 SURVEILLANCE OF ELECTRONIC DATA

In a retrospective, register-based, open cohort study by Abrahamsson et al. [9] aimed at investigating whether prescription of sedatives may be associated with mortality in patients in MAT, time-to-event analyses were used to assess risk of overdose and non-overdose mortality in Swedish residents between the ages of 18-50 who were dispensed methadone or buprenorphine as MAT for opioid dependence (not pain conditions) between July, 2005 and December, 2012 (n= 4,501). Opioid maintenance was assumed to last for 90 days after the last dispensed methadone or buprenorphine prescription, and individuals dispensed an MAT drug without a prescription were not included. Patients remained in the cohort even if they subsequently stopped MAT. Over twenty percent of the sample was dispensed pregabalin (see Table A below), including over 30% of those who died from overdose and 19% of those who died from non-overdose causes (suicide by intentional overdose is included in the non-overdose category). Table B shows the mortality rates per 1,000 person-years for patients with and without pregabalin treatment, and the total person years in each condition.

Table A from Abrahamsson et al.

Description of the study cohort. Characteristics of deceased subjects across causes of death.

	Total sample (n= 4501)	Deceased from overdose (n= 193)	Deceased from other causes (n= 163)	Deceased, all causes of death (n= 356)
Female sex (%)	26.2	18.3	16.8	19.6
Age at baseline (median, IQR)	34.4 (28.7–42.1)	34.0 (28.5–43.0)	42.2 (33.6–46.6)	38.7 (29.9–44.9)
Inpatient treatment for non-fatal overdose ^a (%)	5.0	7.4	4.9	6.2
Inpatient psychiatric treatment ^a (%)	8.1	5.4	11.0	8.1
Inpatient treatment for suicide attempt ^a (%)	6.5	7.9	9.2	8.7
Benzodiazepine treatment ^b (%)	32.4	37.1	40.5	38.8
Z-drug treatment ^b (%)	40.8	49.5	45.4	47.2
Pregabalin treatment^b (%)	22.2	30.2	19.0	25.6

IQR – inter-quartile range.

^a Any episode during the study period.

^b At least one prescription during the study period.

Table B from Abrahamsson et al.

Mortality rates per 1000 person-years.

	Mortality per 1000 person-years			Observed person-years (% of total)
	Overdose death	Non-overdose death	All-cause mortality	
In pregabalin treatment^b	26.2	10.7	36.8	1032 (4.8%)
Not in pregabalin treatment	8.1	7.4	15.6	20,406 (95.2%)

The risk of overdose death associated with pregabalin use compared to no pregabalin use in the full cohort was nearly three times higher (adjusted hazard ratio (AHR) 2.82, CI: 1.79-4.43) (See Table C below). All-cause mortality risk was also increased comparing pregabalin use to no pregabalin use. In adjusted analyses, Z-drug (e.g. zolpidem) use was associated with increased risk of overdose death, and benzodiazepine use was associated with increased risk of non-overdose death (including suicides) and all-cause mortality.

Table C from Abrahamsson et al.

Variables potentially associated with overdose death, non-overdose death, and all-cause mortality. Extended Cox regression analyses.

	Overdose death		Non-overdose death		All-cause mortality	
	HR (95% CI)	AHR (95% CI)	HR (95% CI)	AHR (95% CI)	HR (95% CI)	AHR (95% CI)
Female sex	0.57 (0.39–0.83) [*]	0.58 (0.40–0.85) [*]	0.67 (0.46–0.99) [*]	0.67 (0.46–0.99) [*]	0.62 (0.47–0.81) [*]	0.63 (0.48–0.82) [*]
Age (baseline)	0.99 (0.98–1.01)	1.00 (0.98–1.02)	1.08 (1.05–1.10) [*]	1.08 (1.05–1.11) [*]	1.03 (1.02–1.05) [*]	1.04 (1.02–1.05) [*]
Inpatient treatment for non-fatal overdose ^a	2.73 (1.55–4.83) [*]	1.79 (0.93–3.47)	1.55 (0.76–3.17)	1.09 (0.50–2.34)	2.14 (1.37–3.35) [*]	1.46 (0.87–2.43)
Inpatient psychiatric treatment ^a	1.22 (0.66–2.26)	0.77 (0.40–1.49)	2.19 (1.30–3.67) [*]	1.92 (1.11–3.32) [*]	1.68 (1.13–2.49) [*]	1.24 (0.81–1.9)
Inpatient treatment for suicide attempt ^a	2.48 (1.45–4.22) [*]	1.53 (0.85–2.76)	2.38 (1.37–4.11) [*]	2.49 (1.38–4.51) [*]	2.43 (1.65–3.58) [*]	1.87 (1.22–2.86) [*]
OMT status ^a	0.33 (0.24–0.44) [*]	0.34 (0.25–0.46) [*]	1.04 (0.75–1.45)	0.97 (0.70–1.35)	0.56 (0.45–0.69) [*]	0.55 (0.44–0.68) [*]
Benzodiazepine treatment ^a	2.02 (1.36–2.98) [*]	1.49 (0.97–2.29)	2.44 (1.64–3.62) [*]	2.02 (1.29–3.18) [*]	2.21 (1.67–2.92) [*]	1.75 (1.28–2.39) [*]
Z-drug treatment ^a	1.98 (1.38–2.84) [*]	1.60 (1.07–2.39) [*]	1.42 (0.92–2.20)	0.96 (0.59–1.59)	1.72 (1.3–2.26) [*]	1.28 (0.93–1.75)
Pregabalin treatment^a	3.22 (2.13–4.86) [*]	2.82 (1.79–4.43)[*]	1.37 (0.74–2.55)	1.16 (0.60–2.25)	2.32 (1.65–3.27) [*]	2.01 (1.38–2.91)[*]

HR: Hazard ratio.

AHR: Adjusted hazard ratio.

^a Time-dependent variable.

^{*} p < 0.05.

When the cohort was restricted to time on MAT only, the findings were similar for both overdose death (AHR 2.84, CI: 1.48-5.45) and all-cause mortality (AHR 1.82, CI: 1.10-3.01) comparing pregabalin use to no pregabalin use. In this sub-analysis, benzodiazepine use was no longer associated with all-cause mortality, while Z-drug use was associated with all-cause mortality. When 30-day windows were used to categorize MAT status in sensitivity analyses, the findings were similar with respect to pregabalin.

Peckham et al. [10] used a large commercial claims database (MarketScan) to estimate the prevalence of abuse of gabapentin between the years 2013-2015. Patients between 16-64 years old were included if they had two or more pharmacy claims for one or more of the following medications: alprazolam, gabapentin, pregabalin, zolpidem, or any opioid analgesic medication. Average daily dose was calculated for each patient using days' supply, number of tablets, and dose strength. Calculated average daily doses that exceeded defined dose thresholds were used as a surrogate marker of abuse. The opioid dose threshold was based on a CDC guidance for opioids (50 morphine milligram equivalents), and dose thresholds for gabapentin and pregabalin were 3600 mg and 600 mg, respectively, both based on labeled maximum daily dose. Potential abuse was defined as three or more claims exceeding the daily dose thresholds. After 12-months of continuous enrollment, 3.2% of patients dispensed gabapentin (n=47,480) had three or more claims exceeding the label dose threshold compared to 4.9% of patients dispensed pregabalin (n=6,420). Twenty-four percent of patients used opioids and gabapentin simultaneously (any combination of 3 claims for either drug) (n=15,848), with 28% of patients using opioids and pregabalin simultaneously (n=2,823).

Lorenz curves were also calculated to measure “abuse potential” of gabapentin and pregabalin. Lorenz curves assess cumulative percentage of supply consumed as a function of utilization frequency at a population level. The primary Lorenz curve measure is “Lorenz-1”, which represents the percentage of total drug supply (in terms of milligrams dispensed) consumed by the top 1% of users. Lorenz-1 values were 37% opioids, 19% gabapentin, 15% pregabalin, 14% alprazolam, and 13% zolpidem. A

Lorenz-1 curve of 15% or more (i.e. the top 1% of users consume $\geq 15\%$ of the drug supply) is considered to indicate high potential for abuse.^{xii}

Boden et al [11] and Schjerning et al [12] also looked at patients exceeding dose thresholds as a surrogate marker of potential abuse. In Boden et al, all patients in Swedish national registers dispensed at least three prescriptions of pregabalin between July 2006 and December 2009 were included (n =48,550). The daily dose was defined as the amount of pregabalin dispensed in the second dispensing, divided by the number of days between the second and third dispensings. The dose threshold used in this study was 600 mg, above which was considered potential abuse. Of the patients dispensed pregabalin during the study period, 8.5% were dispensed a dose that exceeded the maximum daily recommended dose. Previous substance use disorder or treatment was present in 20 and 31% of patients dispensed pregabalin within and exceeding the recommended dose range, respectively. Patients at increased risk of being dispensed pregabalin at higher than the defined dose threshold were male (adjusted odds ratio (aOR) 1.40, CI:1.31– 1.49), were between 18 and 29 years of age compared with those aged ≥ 65 years (aOR 1.62, 95 % CI 1.45–1.82), were lower SES (aOR 1.24, 95 % CI 1.10–1.40), had epilepsy (aOR 1.41, 95 % CI 1.10–1.81), had a previous substance use disorder treatment or diagnosis (aOR 1.41, 95 % CI 1.31–1.52) and had previously been dispensed high doses of drugs with abuse potential (aOR 1.77, 95 % CI 1.62–1.94).

Schjerning et al also looked at predictors of pregabalin use above recommended dosage using the Danish nationwide registers from 2004–2013. Daily dose was calculated similar to the other described studies and dose thresholds were defined as “high use” (≥ 600 mg/day) or “very high use” ($\geq 1,200$ mg/day). Out of 42,520 incident pregabalin users, 4,090 (9.6%) were treated with more than 600 mg/day for 6 months and 2,765 (6.5%) for more than 12 months. For “very high dose”, 276 (0.65%) were treated with more than 1,200 mg in 6 months, and 137 (0.33 %) in 12 months. Male gender and prescription of antipsychotics, benzodiazepines, and opioids at baseline were associated with increased risk of use of above the recommended dosage (both dose threshold, and after both 6 and 12 months). The Lorenz-1 curve calculated in this study 6.1%.

Wills et al [13] conducted a retrospective study using electronic poison control center data from Virginia, evaluating clinical outcomes from anticonvulsant overdose, and assessing whether any particular agent appears more toxic in overdose cases. Data from the poison control center database, Toxicall™, was queried using key words “gabapentin,” “lamotrigine,” “levetiracetam,” “tiagabine,” “topiramate,” “zonisamide,” “pregabalin,” and “oxcarbazine” from January 1, 2002 to December 31, 2011. Poison center charts were reviewed by two abstractors looking for pharmaceutical exposure, self-reported dose, clinical effect score, and other clinical data recorded in the chart. Only cases over the age of 15 who had been referred to the hospital were included (n=347). There were 116 gabapentin, 67 lamotrigine, 15 levetiracetam, 15 tiagabine, 56 topiramate, 23 pregabalin, and 55 oxcarbazepine cases. Eighteen percent of gabapentin cases had moderate or severe clinical effects (as deemed by the PCC, see appendix C for

^{xii} Gjerden P, Bramness JG, Slordal L. The use and potential abuse of anticholinergic antiparkinson drugs in Norway: a pharmacoepidemiological study. *Br J Clin Pharmacol.* 2009;67(2):228–33.

definitions), and 10% for pregabalin. The median estimated dose at the time of the event for gabapentin cases was 6,000 mg, and 2,375 mg for pregabalin cases, both well above the maximum recommended daily dose.

3.4.2.1 ELECTRONIC DATA SUMMARY AND LIMITATIONS

The studies using electronic data systems appear to suggest that pregabalin use is associated with higher risk of overdose mortality and all-cause mortality among patients on MAT, and that many patients are dispensed pregabalin and gabapentin above the recommended daily dose range in the U.S. and other developed countries, with and without concomitant opioid dispensing.

These investigations have several important limitations that should be considered. Abrahamsson et al. compared the risk of death during time on pregabalin to time not on pregabalin among MAT patients using a time-varying pregabalin, benzodiazepine, and Z-drug exposure variable. This means that some patients were taking none of the study drugs, while others were taking one, two, or all three, with some cycling between them, and others using various permutations of the three at different times. Since all three drugs/drug classes were associated with increased risk of death, it is possible that the effect estimate comparing pregabalin (and the other drug classes) use to no pregabalin use was diluted (or potentiated depending on possible differential partitioning of study drug exposure person-years) by the effects of the other drug classes, and it is difficult to isolate the effect of pregabalin alone. The authors did not describe any assessment of possible effect modification between concomitant use of pregabalin and any of the other drug classes under study; however, it is unlikely that this would have been possible given the small amount of person-years for pregabalin use relative to no pregabalin use. While the authors adjusted for many relevant covariates, it is still possible that there is residual confounding by indication, whereby patients using pregabalin have other serious conditions for which pregabalin is indicated.

The studies assessing the proportion of patients using above the recommended daily dose of gabapentin and pregabalin are simply assessing utilization patterns of these drugs, not indirect measures of abuse, as these various metrics have not been validated, and no dose threshold that constitutes abuse has been established. Patients may be using above the recommended daily dose as a function of their condition or some other valid clinical reason, unrelated to abuse or diversion.

In regards to the study of the Virginia poison center data, poison control charts are inherently limited. These charts contain self-reported information obtained during the call, but are unreliable in what follow-up information is collected after the call from the treating facility, or patient. Additionally, a self-reported overdose does not necessarily mean that an actual overdose occurred, despite the patient being referred to the hospital for follow-up care.

3.4.3 DRUG-INVOLVED MORTALITY

Several identified studies used data from postmortem toxicological assessments. In a study by Hakkinen et al. [14], all deaths in Finland in which pregabalin or gabapentin was found in postmortem toxicology during 2010–2011 were identified and evaluated.

During 2010– 2011 there were 101,472 deaths in Finland, and an autopsy was performed in 22,421 cases (22.1% of all deaths). Toxicological analyses were performed in 13,766 cases, and only cases with a confirmed positive pregabalin or gabapentin finding were included in this study. All individuals with a pregabalin or gabapentin finding from a postmortem sample (blood or urine), were recorded as cases. Hakkinen et al evaluated the final death certificates and forensic pathologists' referrals individually to assess whether the pregabalin or gabapentin use had been abuse or medical use. Abuse cases were defined as those in which pregabalin or gabapentin had not been prescribed for medical use, and one of the following conditions was met: the decedent was a known drug abuser; there were injection marks or injection equipment near the body; amphetamines, cannabis, GHB or other illicit drugs were found in the toxicological investigation.

Pregabalin was found in 316 cases and gabapentin in 43 cases (See Table D below). Over 48% of the pregabalin cases were defined as abuse compared to 18.6% of the gabapentin cases. Overall, pregabalin poisoning was confirmed in 10.1% of all pregabalin cases, while gabapentin poisoning was confirmed in 4.7% of all gabapentin cases. Pregabalin poisoning accounted for 19.1% of potential pregabalin abuse cases, while gabapentin poisoning accounted for 12.5% of potential gabapentin abuse cases. The median blood concentration of pregabalin was 15 mg/L in the abuser group and 5.8 mg/L in the other cases. For gabapentin, these concentrations were 12 mg/L and 8.3 mg/L, respectively.

Table D from Hakkinen et al

Characteristics of postmortem cases positive for pregabalin (PRG) or gabapentin (GBP) in the abuse and other use groups.

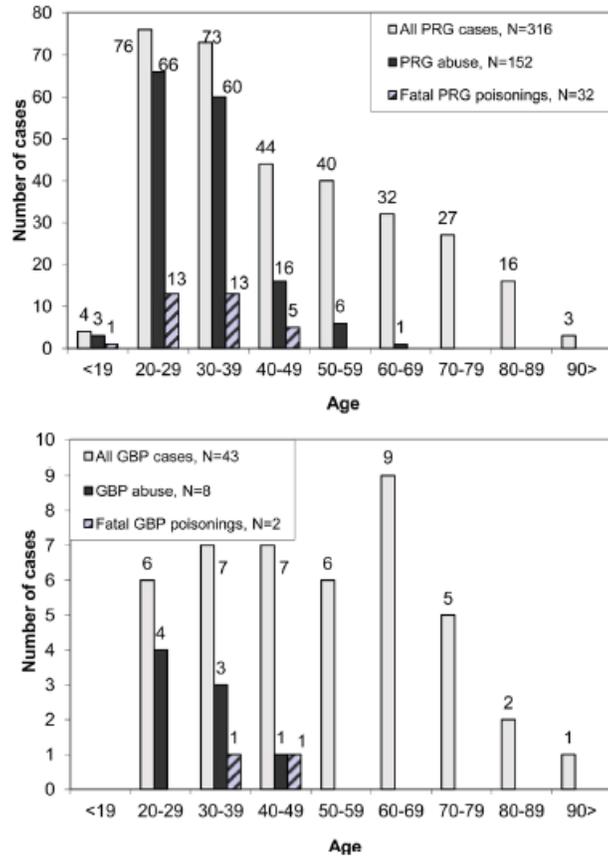
	Cases, N(%)	Poisonings ^a , N(%)	Accidents, N(%)	Age, median (range)	Men, N(%)	Concentration ^b , median (range), mg/L
Abuse						
PRG	152 (48.1)	29 (19.1)	113 (74.3)	30 (18–66)	127 (83.6)	15 (0.43–110)
GBP	8 (18.6)	1 (12.5)	5 (62.5)	30 (24–47)	6 (75.0)	12 (0.62–45)
Other use						
PRG	164 (51.9)	3 (1.8)	36 (22.0)	58 (19–92)	95 (57.9)	5.8 (0.28–110)
GBP	35 (81.4)	1 (2.9)	5 (14.3)	58 (24–94)	24 (68.6)	8.3 (2.7–93)

^a PRG or GBP as the main finding in fatal poisoning.

^b Postmortem concentration in femoral blood.

A majority of the pregabalin cases in the younger age bands (20-29 and 30-39 y/o) were deemed pregabalin abusers, and nearly all of the fatal pregabalin poisonings were among decedents in these younger age bands (See Figure A below). This was similar for gabapentin but there were far fewer fatal gabapentin poisonings.

Figure A from Hakkinen et al: Number of all pregabalin (PRG) and gabapentin (GBP) positive cases, abuse cases and fatal poisonings in different age groups in postmortem cases in Finland in 2010–2011.



In those considered pregabalin abusers, opioids were detected in 91.4% of the cases (See Figure B below). In addition, buprenorphine, methadone, and tramadol were detected disproportionately compared to those not considered abusers; codeine was the same comparing those considered abusers to those who were not, but oxycodone was detected more often in those not considered abusers (See Figure C below). In those considered gabapentin abusers, opioids were detected in 87.5% of cases (See Figure B below).

While it is not known how well these data generalize to the U.S., this study was the only study DEPI is aware of that directly implicates pregabalin and gabapentin alone in unintentional overdose deaths.

Figure B from Hakkinen et al: Number of pregabalin and gabapentin positive cases with an alcohol (ALC) and opioid (OPI) finding in the abuser group and in the other cases group. All the “only pregabalin” or “only gabapentin” cases also included other CNS acting drugs besides pregabalin or gabapentin.

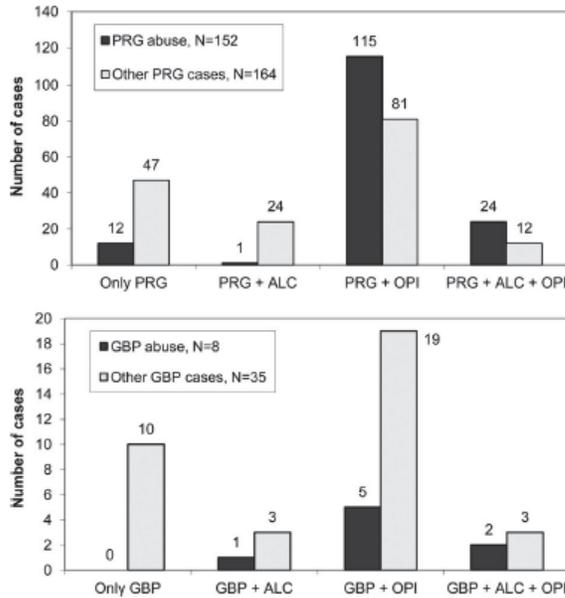
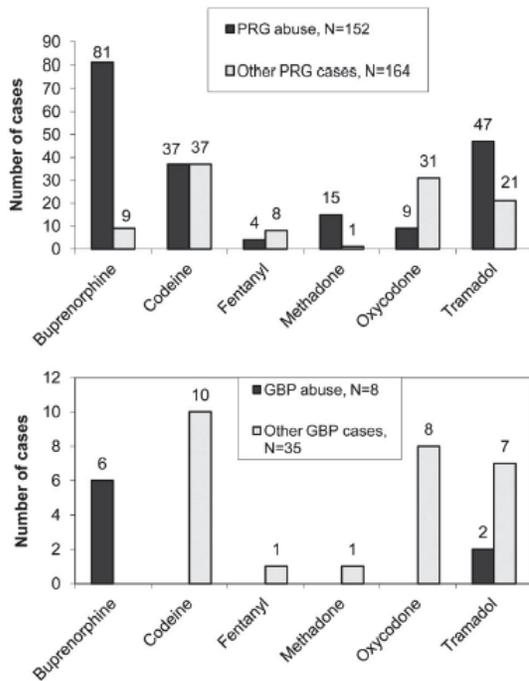
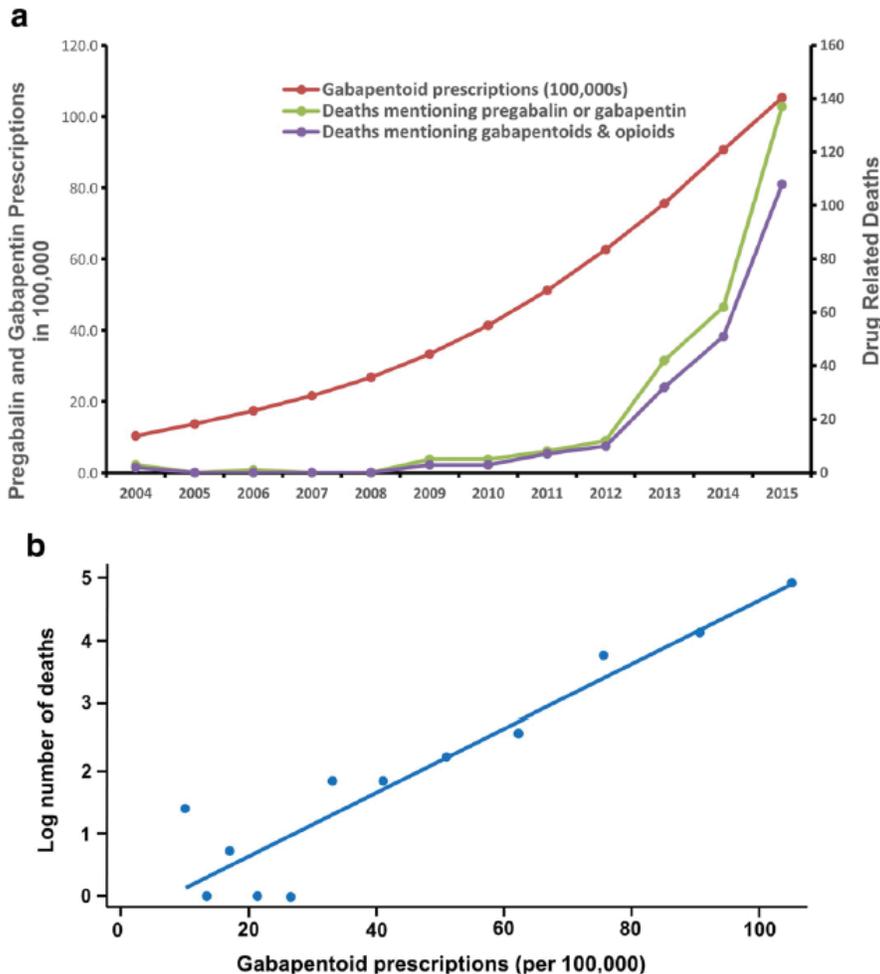


Figure C from Hakkinen et al: Number of pregabalin - and gabapentin -positive cases with an opioid finding in the abuser group compared with the other pregabalin and gabapentin cases.



Lyndon et al [4] (mentioned in 3.4.1) also looked at drug-related deaths in England and Wales involving pregabalin and gabapentin between January 2004 and December 2015 using data from the Office of National Statistics (ONS). The ONS has access only to information specified on the death certificate, and does not have access to the full toxicology report. The number of community prescriptions per year for pregabalin and gabapentin in England and Wales were obtained from the Health and Social Care Information Centre. There has been an annual 24% increase in the number of gabapentinoid prescriptions in England and Wales from approximately 1 million in 2004 to 10.4 million in 2015. Deaths in which pregabalin or gabapentin was mentioned on the death certificate increased from fewer than one per year before 2009 to 137 deaths in 2015 (See Figure D.a below). In 79% of these deaths (216 of 275), opioids (heroin, methadone, other or non-specified) were also mentioned. The increase in deaths was highly correlated with prescribing data (correlation coefficient 0.94; See Figure D.b below). For each 100,000 increase in gabapentinoid prescriptions, the mortality rate (deaths involving pregabalin or gabapentin) increased by approximately 5% [CI: 3-6%].

Figures D.a and D.b from Lyndon et al: Number of pregabalin and gabapentin prescriptions and number of deaths per year in which pregabalin and gabapentin were mentioned on the death certificate from 2004 to 2015.



Jones et al. [15] assessed pharmaceutical overdose deaths in the U.S. in 2010 using data from the National Vital Statistics System multiple cause-of-death file, which is based on death certificates submitted by medical examiners or coroners. Deaths related to pregabalin and gabapentin were not specifically noted in these analyses; however, deaths related to the drug classes antiepileptic and antiparkinsonism (T42.0-T42.2, T42.5-T42.8), of which pregabalin and gabapentin are described, were noted. Of the 22,134 deaths where specific classes of pharmaceuticals were noted, 1,717 (7.8%) involved antiepileptic and antiparkinsonism drugs. Of the 16,651 deaths involving opioid analgesic drugs, 1,125 (6.8%) involved antiepileptic and antiparkinsonism drugs. Over 65% of all deaths involving antiepileptic and antiparkinsonism drugs also involved an opioid.

3.4.3.1 DRUG-INVOLVED MORTALITY DATA SUMMARY AND LIMITATIONS

Data from the referenced drug-involved mortality studies indicate that gabapentinoids are implicated in drug overdose deaths among those who may be directly abusing the drugs in several developed countries. Mortality rates from overdose involving gabapentinoids may be increasing over time, and opioid analgesics are noted in a significant proportion of gabapentinoid-involved overdose deaths.

These studies, and mortality data, in general, have limitations to consider. In Hakkinen et al, those who were deemed “abusers” may not have been abusing pregabalin or gabapentin as the definition was not validated. Quality mortality data are dependent on complete and thorough postmortem examinations by either a medical examiner or coroner. Decisions as to the involvement of a given drug, or a given quantity of drug, and the intentionality of the decedent, are not always made consistently across examiners, and time. The processes and laws relating to mortality and drug-involved mortality investigations differ by country, and it is not clear how well the results from the Hakkinen et al and Lyndon et al studies generalize to the U.S. While Jones et al looked at pharmaceutical-involved mortality data in the U.S., antiepileptic and antiparkinsonism drugs were grouped together, so how much pregabalin or gabapentin contributed to the deaths is not known.

3.4.4 SUMMARY OF PHARMACOVIGILANCE STUDIES

Five European-based pharmacovigilance studies using spontaneously reported adverse drug reaction (ADR) data were identified and reviewed; however, these types of data systems are better for signal detection as there is no denominator (known population at risk), and are generally not appropriate for signal confirmation, particularly for abuse-related events. These types of data collection systems rely on passively reported adverse events from the public, health care professionals, or pharmaceutical manufacturers and many reports lack critical information about the exposure event. There is mandatory reporting of ADRs by sponsors, but reporting requirements and practices change over

time. Reports from the public or health care professionals can be stimulated by media reports or publicized regulatory actions.

The five identified studies used data mining methods to find cases, and several different methods for calculating disproportionate reporting rates. One study^{xiii} from Sweden using the Swedish national register of adverse drug reactions (SWEDIS), and one study^{xiv} from Germany using the German Federal Institute for Drugs and Medical Devices (BfArM) both found a clear abuse signal for pregabalin. In a study^{xv} using European Medicines Agency's EudraVigilance database, both pregabalin and gabapentin had abuse signals. Finally, in two studies from France using the French Pharmacovigilance System, one study^{xvi} found an abuse signal for both pregabalin and gabapentin (years 1995-2009), while another^{xvii} did not find an abuse signal for pregabalin (years 2010-2015). The authors of the study where an abuse signal for pregabalin was not observed explicitly note, "*Considering evidence of pregabalin abuse worldwide, this analysis underlines the limitations of spontaneous reporting system in the field of addictovigilance.*"

4 OVERALL DISCUSSION

Pregabalin is a scheduled drug with a known, labeled abuse potential. In a clinical abuse liability study of 16 healthy volunteers by Zacny et al^{xviii}, pregabalin produced dose-related increases in some subjective effects, but "drug liking" was not different from placebo for either 75mg or 150mg of administered pregabalin. Similarly, when pregabalin was combined with oxycodone (10 mg), subjective effects were also enhanced, but "drug liking" did not increase relative to oxycodone alone. While pregabalin has a similar mechanism of action to gabapentin, they have slightly different pharmacokinetic profiles.^{xix} It has been hypothesized that because of its rapid absorption and onset of action, the abuse potential of pregabalin is likely greater than that of

^{xiii} Schwan S et al. (2010) A signal for an abuse liability for pregabalin—results from the Swedish spontaneous adverse drug reaction reporting system. *Pharmacoepidemiology and Prescription*, 66: 947-953.

^{xiv} Gahr M et al. (2013) Pregabalin abuse and dependence in Germany: results from a database query. *Pharmacoepidemiology and Prescription*, 69: 1335-1342

^{xv} Chiappini S et al. (2016) A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. *CNS drugs*, 30: 647-654.

^{xvi} Fuzier R et al. (2013) Adverse Drug Reactions to Gabapentin and Pregabalin: A review of the French Pharmacovigilance Database. *Drug Safety*, 36: 55-62.

^{xvii} Bossard JB et al. (2016) Disproportionality Analysis for the Assessment of Abuse and Dependence Potential of Pregabalin in the French Pharmacovigilance Database. *Clinical Drug Investigation*, 36: 735-742.

^{xviii} Zacny JP et al. (2012) Subjective, Psychomotor, and Physiological Effects of Pregabalin Alone and in Combination With Oxycodone in Healthy Volunteers. *Pharmacol Biochem Behav*, 100(3): 560-565.

^{xix} Bookbrader HN et al. (2010) A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin. *Clinical Pharmacology*, 49(10): 661-669.

gabapentin.^{xx} This is not borne out in the postmarketing data; however, those data do suggest that both gabapentinoids are abused and misused, particularly among those who abuse or misuse opioids, and those on medication assisted treatment (MAT). These drugs are abused both alone and simultaneously with opioids, and/or CNS depressants. While the data are limited as postmarketing research in this area is still in its nascent stages, it is also possible that the abuse or misuse of gabapentinoids is increasing over time.

Abuse of these drugs does not yet appear widespread; nonetheless, utilization of the gabapentinoids continues to increase, most notably for gabapentin, with a significant proportion being prescribed for off-label indications^{xxi}, and with concomitant opioid analgesics (~19% for pregabalin and ~14% for gabapentin in 2016) and MAT products, such as methadone and buprenorphine. It is unclear how the introduction of a higher strength, extended-release (ER) pregabalin product will affect the market. It is possible that utilization will increase for pregabalin (currently there are (b) (4) prescriptions dispensed and ~ (b) (4) unique patient recipients per year for pregabalin) with the introduction of a new product with an extended-release mechanism. It is also possible that an ER pregabalin product will simply be substituted for immediate-release (IR) pregabalin in some subset of patients, not changing the overall utilization. Regardless, utilization for pregabalin is likely to increase over the coming years, as it has at least since 2012, with unknown consequences to both those who are legitimately prescribed the product and those who abuse it.

Some of the effects of increased utilization for both gabapentin and pregabalin can be seen in calls to PCCs over time. For both gabapentinoids, as utilization increased since 2012, calls to PCCs regarding exposure to pregabalin or gabapentin (alone or in combination with other drugs) increased, as have medical outcomes related to the exposures deemed moderate, major and/or death. When normalized by prescriptions dispensed, pregabalin and gabapentin had relatively similar single-substance calls, calls with concurrent opioid exposure, and total exposure calls per 100,000 prescriptions dispensed, and these rates remained relatively consistent throughout the study period. Increases in the absolute numbers of single-substance and total exposure calls have been driven largely by intentional exposures for both pregabalin and gabapentin, including abuse or misuse, as opposed to unintentional exposures or adverse reactions. The annual number of calls where opioids were mentioned along with pregabalin or gabapentin have remained relatively stable from roughly 2008 onward; however, the proportion of all calls for pregabalin and gabapentin involving opioids have decreased in recent years.

There also appears to be increases in the estimated number of non-abuse related ED visits associated with gabapentin exposure as evidenced by the nationally projected data from NEISS-CADES. This may be due, in part, to increases in utilization. When normalized by prescriptions dispensed, rates of non-abuse related ED visits for gabapentin exposures per 100,000 prescriptions dispensed in 2015 appear slightly lower than in 2012. This is

^{xx} Hakkinen M (2014) Profiles of pregabalin and gabapentin abuse by postmortem toxicology. *Forensic Science International*, 241: 1-6.

^{xxi} Goodman CW, Brett AS (2017) Gabapentin and Pregabalin for Pain — Is Increased Prescribing a Cause for Concern? *NEJM*, 377, 5: 411-414.

not true for pregabalin as there were increases in ED visit estimates from 2012 to 2015 with a relatively stable number of prescriptions dispensed over that same period. The number of non-abuse related ED visits associated with pregabalin may change with the introduction of an ER pregabalin product with higher dosage strengths, but whether the number of ED visits per prescriptions dispensed continues to increase over time is unclear. Data from the literature show that many pregabalin and gabapentin patients in the U.S. (and other developed countries) are legitimately dispensed prescriptions that suggest higher than recommended maximum daily doses (estimates ranging from ~5% - 9%). In one study, these patients were more likely to have a substance abuse disorder, or be in treatment for one (Schjerning et al). This potential over-dosage could also lead to non-abuse related adverse drug events requiring medical attention. The NEISS-CADES figures represent non-abuse adverse drug events in the general population and likely reflect use for legitimate clinical needs, but many high risk individuals are also prescribed these drugs or obtain them illegally with the sole purpose of misuse or abuse.

While surveys of gabapentinoid abuse in the general population have not yet been conducted, surveys of high risk individuals suggest that gabapentinoid misuse and abuse is prevalent among those who abuse prescription opioids and heroin, and those in treatment for substance abuse, including MAT. Despite the lack of effect seen by Zacny et al, patients abusing opioids or taking MAT appear to use them for the additive euphoric effect, and the clandestine/illegal market for these drugs may be expanding. Both the Buttram et al. and Smith et al. studies appear to show increases in recent years in the reporting of diversion and misuse/abuse of gabapentin, respectively. While the clandestine/illegal market may be expanding, many high risk patients are also directly prescribed these drugs by health care professionals. In a study by Abrahamsson et al. of Swedish nationals, those on MAT using pregabalin had nearly a 3 times higher risk of death from overdose, and nearly a 2 times higher risk of death from any cause compared to those not using pregabalin.

Mortality data from Finland (Hakkinen et al) show that of the decedents who were positive for pregabalin or gabapentin, almost half of those who were positive for pregabalin at the time of death were possible abusers of pregabalin, and almost one fifth of those positive for gabapentin were possible abusers of gabapentin. Fatal pregabalin poisoning accounted for over 10% of all decedents where pregabalin was detected, and fatal gabapentin poisoning accounted for almost 5% of decedents where gabapentin was detected. In the vast majority of the decedents who were defined as pregabalin abusers in this study, opioids were also detected. Deaths in which gabapentinoids were mentioned alone, or with opioid drugs (heroin, methadone, prescription opioids), have increased dramatically in the U.K. (Lyndon et al.), as well, and these increases are highly correlated with increases in gabapentinoid utilization. It is unclear how well these data from Europe generalize to the U.S., but if they do, it is notable that gabapentinoids are implicated in many drug overdose deaths, overdose death involving gabapentinoids may be increasing, and opioids are detected in a significant proportion of these cases.

It is unknown how the Agency's 2016 enhanced warnings around the concomitant use of benzodiazepines and opioid analgesics will impact the prescribing of gabapentinoids moving forward. It is possible that these enhanced warnings may inadvertently shift many more patients to gabapentinoids with or without concomitant opioid analgesics, but

this is entirely speculative. In general, the use of these drugs is increasing, and while the proportion of office-based visits where opioids are also mentioned along with pregabalin or gabapentin may not have increased since 2012, a significant proportion of patients may use these drugs concurrently. It is clear that those who abuse opioids or are in treatment for opioid abuse (MAT or otherwise) are at risk of gabapentinoid misuse or abuse, and the consequences can be fatal. Whether the addition of a higher milligram strength ER pregabalin product will have a deleterious effect on the continuing opioid abuse problem in the U.S. is unknown, but current data suggest that pregabalin misuse or abuse is prevalent among high risk opioid users, even if the intent of the misuse or abuse is not always clear.

As a tier V scheduled drug, there is evidence that pregabalin alone has abuse potential, and this is apparent from post-marketing data where pregabalin is reported in intentional abuse exposure calls to poison control centers and as the implicated drug in a fatal poisonings, both of which may be increasing over time. That said, the data and literature in regards to the gabapentinoid misuse and abuse is still very limited and fleshing out trends in these data are challenging. No definitive conclusions can be made on the projected public health burden associated with the misuse and abuse of ER pregabalin, but it is highly likely that it will be misused and abused in patients who are either prescribed this drug alone or with opioid therapy, including MAT, perhaps to a greater extent than the lower dosage strength IR pregabalin formulation. Given the concerns around opioid analgesics, post-market required studies should be considered for ER pregabalin and all other pregabalin products in an attempt to understand the risks associated the use of pregabalin with and without concomitant opioid analgesics. Additionally, enhanced warning about the risks of misuse, abuse, addiction, overdose and death associated with pregabalin, and the risks associated with concurrent pregabalin and opioid use (analgesic and MAT), should be considered for all pregabalin product labels. While gabapentin was not the impetus for this review, we did assess data and literature on gabapentin for context and found data suggestive of misuse and abuse with and without concomitant opioid analgesics. Data on gabapentin misuse and abuse are also limited, but given the similarities with pregabalin in indication, utilization, reporting of intentional exposures from poison control centers, and involved fatal poisonings, post-market required studies and enhanced labeling are also warranted for gabapentin products and should be considered.

5 CONCLUSIONS

Pregabalin is a controlled substance with a known abuse potential. Post-marketing data suggest that pregabalin is misused and abused alone, and in combination with opioid analgesics and MAT products. The consequences of misuse or abuse of pregabalin, with or without opioid analgesics or MAT products, can be fatal. Utilization of pregabalin is increasing, albeit modestly, but the impact of the introduction of an ER pregabalin product to the market is unclear. Given the uncertainty in how the pregabalin market will react to a new formulation, that the abuse of ER pregabalin is likely, and that pregabalin products may be prescribed concomitantly with opioid analgesics, DEPI recommends considering post-market required studies with approval of ER pregabalin to understand the risks associated the use of ER pregabalin with and without concomitant opioid

analgesics. Post-market required studies should be considered for the IR pregabalin, as well as gabapentin products, given their similarities with pregabalin products in indication, utilization, and post-market reporting of abuse and misuse, and their consequences. DEPI also recommends considering enhanced warnings in the label for all pregabalin and gabapentin products regarding the risks of misuse, abuse, addiction, overdose and death, and the risks associated with concurrent opioid use (analgesic and MAT).

6 RECOMMENDATIONS

DEPI recommends that post-market required studies be considered to understand the use and misuse/abuse of ER pregabalin (Lyrica CR), with and without concomitant prescribing of opioid analgesic and MAT products. The objectives of these studies are to understand the extent of off-label use, and to capture data on the misuse and abuse of ER pregabalin, and their clinical consequences, in both long-term and short-term users. Post-marketing data suggest that pregabalin is reported in intentional abuse exposure calls to poison control centers, and as the implicated drug in a fatal poisonings (Hakkinen et al. & Abrahamsson et al), both of which may be increasing over time. The post-market required studies should also be considered for IR pregabalin. The risks associated with the use of pregabalin, with and without concomitant use of opioid analgesics, and the risk factors for nonmedical use of pregabalin are not entirely clear. More and better quality data are needed to understand the public health burden associated with pregabalin, and post-market required studies are a vehicle to generate necessary safety data in this area.

DEPI also recommends considering enhanced warnings in the label for all pregabalin products regarding the risks of misuse, abuse, addiction, overdose and death associated with pregabalin. In addition, enhanced warnings about the risks associated with concurrent pregabalin and opioid use, both analgesic and MAT products, should be considered for all pregabalin products. Recommended language for the label surrounding both concerns would need to be carefully considered as to not overstate what the current data suggest given its limitations.

In regards to gabapentin products, given their similarities with pregabalin products in indication, utilization, and post-market reporting of abuse and misuse, and their consequences, post-market required studies and enhanced labeling are also warranted for gabapentin products and should be considered.

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8 APPENDIX A: DRUG UTILIZATION DATABASE DESCRIPTIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches^{xxii}, extended units^{xxiii}, and share of market. These data are based on national projections.

Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over (b) (4) (b) (4) prescription claims per year, captured from a sample of the universe of approximately (b) (4) pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly (b) (4)% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately (b) (4)% (varies by class and geography) of mail service pharmacies and approximately (b) (4)% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over (b) (4) prescription claims per year.

^{xxii} Eaches is represented by multiplying the pack size by the number of units. Package size refers to the number of individual units contained in a package of a particular product type.

^{xxiii} Extended units are the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit. This number is calculated by multiplying the number of units by the product size.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over (b) (4) office-based physicians representing (b) (4) specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over (b) (4) pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

9 APPENDIX B: DRUG UTILIZATION TABLES

Table 1a

Nationally estimated number of dispensed prescriptions for pregabalin and gabapentin^a from U.S. outpatient retail pharmacies

	2012		2013		2014		2015		2016	
	TRx	Share	TRx	Share	TRx	Share	TRx	Share	TRx	Share
Total Prescription	(b) (4)									
Pregabalin										
Gabapentin										

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted May 2017.

^a Gabapentin includes gabapentin encarbriil (gabapentin prodrug)

Table 2a

Nationally estimated number of patients * who received a dispensed prescription for pregabalin and gabapentin, stratified by age, from U.S. outpatient retail pharmacies

	2012		2013		2014		2015		2016	
	Patients	Share								
Total Patients	(b) (4)									
Pregabalin										
0-17 years										
18-64 years										
65 years and older										
Unknown age										
Gabapentin										
0-17 years										
18-64 years										
65 years and older										
Unknown age										

Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted May 2017.

^a Gabapentin include gabapentin encarbriil (gabapentin prodrug)

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

10 APPENDIX C: AAPCC VARIABLE DEFINITIONS

MEDICAL OUTCOME:

No Effect: The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.

Minor Effect: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

Moderate Effect: The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

Major Effect: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.

Death: The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only include those deaths which are probably or undoubtedly related to the exposure. A fatality verification is required. Also include deaths in which the exposure was a contributing factor in the death. For deaths determined to be unrelated to the exposure (those in which the most clinically significant clinical effects are coded as unrelated) the outcome is coded as “Unrelated effect” (the exposure was probably not responsible for the effect[s]).

Other – Includes sub-categories:

Case not followed to a known outcome: In some circumstances it is not appropriate or possible to follow a patient to a reasonably certain medical outcome. In these instances, choose one of the following:

Not followed, judged as nontoxic exposure: The patient was not followed, per clinical judgment the exposure was likely to be nontoxic because the agent involved was nontoxic. The amount implicated in the exposure was insignificant (nontoxic), and/or the route of exposure was unlikely to result in a clinical effect. If this response is selected, there must be reasonable certainty that the patient will not experience any clinical effect from the exposure. Cases that refused follow-up if the exposure was judged as nontoxic may also be included.

Not followed, minimal clinical effects possible: The patient was not followed because, per clinical judgment, the exposure was likely to result in only minimal toxicity of a trivial nature. If this response is selected, the poison center must be reasonably certain, in a worst case scenario, that the patient will experience no more than a minor effect. Cases that refused follow-up if the exposure would possibly result in minimal clinical effects and would cause no more than a minor effect may also be included.

Unable to follow, judged as a potentially toxic exposure: The patient was lost to follow-up (or the poison center neglected to provide follow-up) and per clinical judgment the exposure was significant and may have resulted in toxic manifestations with A MODERATE, MAJOR OR DEATH OUTCOME.

Exposure not responsible for the effect: This category is provided for those patients who exhibit clinical effects, which in the final analysis are determined unrelated to a toxic problem.

Unrelated Effect: Based upon all the information available, the exposure was probably not responsible for the effect(s). If this response is selected, all coded clinical effects must be coded as “unrelated”.

REASON:

Unintentional: An unintentional exposure results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight coding options are available for unintentional exposures. (Includes sub-categories: *General; Environmental; Occupational; Therapeutic Error; Misuse; Bite/Sting, Food Poisoning; Unknown*)

Intentional: A purposeful action results in an exposure. The following four categories relate to intentional exposures. (Includes sub-categories: *Suspected Suicidal; Misuse; Abuse; Unknown*)

Adverse Reaction: This category is used to monitor adverse reactions (experiences) to a variety of products, including drugs, foods, cosmetics and industrial or household chemicals. (Includes sub-categories: *Drug; Food; Other*)

Other/Unknown: This category is used when the reason for the exposure cannot be determined or if no other category is appropriate. (Includes sub-categories: *Contaminant/Tampering; Malicious; Withdrawal; Unknown*)

11 APPENDIX D: AAPCC TABLES

All (including “related” and “unrelated”) medical outcomes (See AAPCC methods for definitions) for pregabalin and gabapentin single-substance and total exposure calls from 2004 through 2016 are displayed in Table 4a. The number of pregabalin single-substance and total exposure calls with medical outcomes increased sharply after market approval, from 2005 to 2008. Subsequently, the number and proportion of exposure calls with medical outcomes remained fairly stable between 2008 to 2016. Pregabalin single-substance exposure were classified as minor effect (n= (b) (4)), moderate effect (n= (b) (4)), major effect (n= (b) (4)) and death (n= (b) (4)) [no effect (n= (b) (4)) and unknown effect (n= (b) (4))]. A higher proportion of total pregabalin exposure calls (n= (b) (4)) were reported to have medical outcomes (minor, moderate, major, or death) compared to single-substance exposures (n= (b) (4) %). Total exposures were classified as minor effect (n= (b) (4) %), moderate effect (n= (b) (4) %), major effect (n= (b) (4) %) and death (n= (b) (4) %) [no effect (n= (b) (4) %) and unknown effect (n= (b) (4) %)].

Medical outcomes associated with single-substance and total gabapentin exposure calls were higher in number, but similar in proportion, compared to those from pregabalin exposure. The number of medical outcomes for single-substance and total exposure calls for gabapentin fell slightly between 2004 to 2007, then increased every year through 2016. Gabapentin single-substance exposures were classified as minor effect (n= (b) (4)), moderate effect (n= (b) (4)), major effect (n= (b) (4)) and death (n= (b) (4)) [no effect (n= (b) (4)) and unknown effect (n= (b) (4))]. Similarly to pregabalin, a higher proportion of total gabapentin exposure calls (n= (b) (4)) reported medical outcomes compared to single-substance calls (n= (b) (4) %). Medical outcomes reported for total gabapentin exposures were classified as minor effect (n= (b) (4) %), moderate effect (n= (b) (4) %), major effect (n= (b) (4) %) and death (n= (b) (4) %) [no effect (n= (b) (4) %) and unknown effect (n= (b) (4) %)].

Table 4a: Frequencies for Pregabalin and Gabapentin exposures with medical outcomes, not restricted to outcomes related to exposure

Drug Year	Medical Outcome										
	Single Substance Exposure Calls					Total Exposure Calls					
	No Clinical Effect	Minor Effect	Moderate Effect	Major Effect	Death	No Clinical Effect	Minor Effect	Moderate Effect	Major Effect	Death	Unknown Effect
Pregabalin											(b) (4)
2005											
2006											
2007											
2008											
2009											
2010											
2011											
2012											
2013											
2014											
2015											
2016*											
2018*											
Gabapentin											
2004											
2005											
2006											
2007											
2008											
2009											
2010											
2011											
2012											
2013											
2014											
2015											
2016*											
2018*											

*Data year not locked

12 APPENDIX E: NEISS-CADES TABLE

Table 5a: National estimates of ED visits from NEISS-CADES

	National projections of non-abuse-related ED visits (Confidence interval)										
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Pregabalin (Total)											(b) (4)
Gabapentin (Total)											
Gabapentin (Unintentional overdos											

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ALEX SECORA
09/07/2017

JENNIE Z WONG
09/07/2017

RICHARD S SWAIN
09/07/2017

RAJDEEP K GILL
09/07/2017

JACQUELINE M PUIGBO
09/07/2017

CYNTHIA J KORNEGAY
09/07/2017

GRACE CHAI
09/07/2017

JUDY A STAFFA
09/07/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 31, 2017

To: Shelly Kapoor, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 209501
OPDP labeling comments for LYRICA[®] CR (pregabalin) extended-release
tablets, for oral use, CV
Labeling Review

OPDP has reviewed the proposed package insert (PI) and Medication Guide and carton and container labeling for LYRICA[®] CR(pregabalin) extended-release tablets, for oral use, CV (Lyrica CR) that was submitted for consult on February 3, 2017. Comments on the proposed PI and Medication Guide are based on the version sent via email from Shelly Kapoor (RPM) on August 17, 2017 entitled "Working Label 10-Aug-2017.doc" and the draft carton/container labeling submitted on December 15, 2016

Comments regarding the PI are provided on the marked version below.

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LATOYA S TOOMBS
08/31/2017

Clinical Inspection Summary

Date	August 29, 2017
From	Damon Green, M.D., M.S., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shelly Kapoor, Regulatory Project Manager Lisa Wiltrout, M.D., Clinical Reviewer Robert Shibuya, M.D., Clinical Team Lead Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	209501
Applicant	Pfizer, Inc.
Drug	Lyrica® CR (Pregabalin)
NME (Yes/No)	No
Therapeutic Classification	Neuropathic Analgesic and Anticonvulsant
Proposed Indication(s)	Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), management of post-herpetic neuralgia (PHN) and management of Fibromyalgia (FM)
Consultation Request Date	March 3, 2017
Summary Goal Date	August 29, 2017
Action Goal Date	October 13, 2017
PDUFA Date	October 15, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Agafina, Shilkina, Nadashkevich, and Tayob were inspected in support of this NDA. The final classification of the inspections of Drs. Agafina and Shilkina, and the preliminary classification of Dr. Nadashkevich were NAI. The preliminary classification of Dr. Tayob was VAI. Based on the results of the clinical investigator inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective application.

Observations for the clinical sites of Drs. Nadashkevich and Tayob are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

II. BACKGROUND

Pfizer, Inc., sponsor of NDA 209501 is seeking approval of Pregabalin (LYRICA®) Extended Release (ER) tablets for the Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), management of post-herpetic neuralgia (PHN), and management of Fibromyalgia (FM).

Inspections were requested for study **Protocol A0081224** entitled, “A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of Once Daily Controlled Release Pregabalin in the Treatment of Patients with Postherpetic Neuralgia.” The sites chosen had the highest level of subject enrollment for the double blind (DB) phase of the trial. The DB phase of the trial was the driving factor for efficacy determination.

The study was performed in 17 countries, at 129 centers (68 Centers in the U.S.). The first subject’s first visit was on 08 April 2011, and the last subject’s last visit was on 03 September 2014. A total of 1117 subjects were screened, of which 801 subjects entered the single blind phase, leading to 418 subjects entering the double blind phase.

The primary efficacy endpoint for the study was the time to loss of therapeutic response (LTR), defined as <30% pain response relative to the baseline phase (based on a 7 day average of daily pain diary) or subject discontinuation due to lack of efficacy or adverse events (AEs), in the DB phase of the study. The sponsor concluded that the Kaplan-Meier analysis of the primary endpoint showed that the time to LTR was statistically significantly longer with Pregabalin CR as compared to placebo. Fewer Pregabalin CR treated subjects, 13.9% (29 of 208 subjects) experienced LTR during the DB phase compared to placebo treated subjects, 30.7% (63 of 205 subjects).

III. RESULTS (by site):

Name of CI, Address, Country if non-U.S. or City, State if U.S.	Protocol #, Site #, and # of Subjects	Inspection Date	Classification
Alina S. Agafina St. Petersburg State Healthcare Institution City Hospital #40 Kurortnogo Administrativnogo Rajona Lit. B, 9 Borisova ulitsa, Sestroretsk Saint-Petersburg 197706	Protocol: A0081224 Site: 1035 Subjects: -Total enrolled 40 -DB phase 36	07/10/2017- 07/14/2017	NAI

RUSSIAN FEDERATION			
Nataliya P. Shilkina State Budgetary Health Institution of Yaroslavl region “Clinical hospital #10” 12 Gagarina Street Yaroslavl 150023 RUSSIAN FEDERATION	Protocol: A0081224 Site: 1032 Subjects: -Total enrolled 19 -DB phase 16	7/17/2017 – 7/19/2017	NAI
Oleg Nadashkevich Regional Municipal Dermatovenerologic Dispensary Polyclinic Care, Family Medicine and Dermatology Venereology Dpt. of Lviv, NMU n.a. Danylo Galytskyy 1 Konovaltsya Street, Lviv 79013 UKRAINE	Protocol: A0081224 Site: 1140 Subjects: -Total enrolled 26 -DB phase 20	8/07/2017 – 8/11/2017	Pending; Interim Classification: NAI
Mohammed Siddique Tayob Mzansi Ethical Research Centre 186 Cowen Ntuli Street Middleburg 1050 SOUTH AFRICA	Protocol: A0081224 Site: 1011 Subjects: -Total enrolled 42 -DB phase 35	6/26/2017 – 6/30/2017	Pending; Interim Classification: VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations; Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Alina S. Agafina

Dr. Agafina is a neurologist at the St. Petersburg State Healthcare Institution (City Hospital #40) in St. Petersburg, Russia, and the Head of the Clinical Research Department. Under Protocol A0081224, 44 subjects were screened, 40 subjects were enrolled, with 36 completing the double-blind phase of the study. The informed consent, adverse events, inclusion criteria, and primary efficacy endpoint (pain scores) for all 40 subjects were reviewed during the inspection. The inclusion/exclusion criteria were verified through the review of laboratory results (bloodwork) and ECG scans, which were part of the medical records for the subjects in the study. The audited data at the clinical site showed no discrepancies between the source document data and the data that was submitted by the sponsor.

There were no significant observations made during the inspection; therefore no FDA-483 was issued. Overall, the study appears to have been conducted without violation in data integrity or subject safety and well-being. The data generated by this site appears acceptable in support of this current application.

2. Dr. Nataliya P. Shilkina

Dr. Shilkina is a cardiologist and rheumatologist at the State Budgetary Health Institution of Yaroslavl Region (Clinical Hospital #10) in Yaroslavl, Russia. Under Protocol A0081224, 19 subjects were screened, 19 subjects were enrolled, with 16 completing the double-blind phase of the study. The informed consent, adverse events, inclusion criteria, and primary efficacy endpoint (pain scores) for all 19 subjects were reviewed during the inspection. The inclusion/exclusion criteria were verified through the review of laboratory results (bloodwork), and ECG scans which were part of the medical records for the subjects in the study. The audited data at the clinical site showed no discrepancies between the source document data and the data that was submitted by the sponsor.

There were no significant observations made during the inspection; therefore no FDA-483 was issued. Overall, the study appears to have been conducted without violation in data integrity or subject safety and well-being. The data generated by this site appears acceptable in support of this current application.

3. Dr. Oleg Nadashkevich

The inspection is complete although the EIR is pending. Preliminary communication from the inspector reveals that no significant regulatory violations were found, and no FDA-483 was issued. It should be noted that the primary efficacy endpoint data were not verified at this site because the electronic phone diaries used to collect subject pain and sleep data were kept in the CRO's possession (only an eCRF disk and a copy of the clinical study report was provided to the investigator at study closure).

4. Dr. Mohammed Siddique Tayob

The inspection is complete though the EIR is pending. Preliminary communication from the inspector reveals minor regulatory deviations, and a FDA-483 was issued:

Observation 1: investigation was not conducted in accordance with the investigational plan.

- One subject experienced two adverse events at separate times: follicular tonsillitis and a "gritty" feeling in right eye. Both events went unreported to the sponsor.
- For one subject, the Suicidality Severity Rating Scale, which should be completed at each visit, was incomplete, though negative responses were recorded on the CRF by the study coordinator.
- For three subjects, prior and concomitant medications were not reported to the sponsor as outlined in the investigational plan.

Observation 2: investigational drug disposition records are inadequate with respect to dates, quantity, and use by subjects.

- For one subject, the site failed to clearly identify the investigational product used, quantities of investigational product used, and dispensing and return date(s) of the investigational product.

{ See appended electronic signature page }

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Susan Thompson, M.D.
Team Leader,
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Division of Clinical Compliance Evaluation
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Kassa Ayalew, M.D., M.P.H
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Office of Scientific Investigations

cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Shibuya
DAAAP /Project Manager/ Kapoor
DAAAP/Medical Officer/Wiltrout
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Thompson
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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08/29/2017

SUSAN D THOMPSON
08/29/2017

KASSA AYALEW
08/29/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: June 23, 2017

Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 209501

Product Name and Strength: Lyrica CR (pregabalin) extended release tablets
82.5 mg, 165 mg and 330 mg

Product Type: Single ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Pfizer, Inc.

Submission Date: December 15, 2016

OSE RCM #: 2016-2970

DMEPA Primary Reviewer: Nasim Roosta, PharmD

DMEPA Team Leader: Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review documents our evaluation of the proposed Prescribing Information, Medication Guide, container label, and carton labeling from a medication error prospective. Pfizer submitted NDA 209501, which would introduce the addition of Lyrica CR (pregabalin) extended release tablets.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed Medication Guide, Prescribing Information (PI), container labels, and carton labeling for Lyrica CR to determine if they are acceptable from a medication error perspective.

We performed a risk assessment of the proposed Prescribing Information, Medication Guide, container label and carton labeling to identify deficiencies that may lead to medication errors and to identify other areas that can be improved. We searched the Institute for Safe Medication Practices (ISMP) newsletters to inform our review of the labels and labeling and our search found one medication error case involving incorrect dosing for a renally impaired patient, caused by confusion related to the renal dosing table included in the currently approved Prescribing Information for Lyrica. In our search for past DMEPA reviews, we found a postmarketing review (OSE RCM # 2011-4313) that also described cases of patients with reduced renal function who receive higher than recommended starting dose of Lyrica. The

cause for higher doses in renally impaired patients could not be determined. However, we recommended changes to the renal dosing guidelines in the Lyrica PI. One of the recommendations was to revise the renal dose modification table and to evaluate the revisions in a labeling comprehension study. In response to our recommendations, Pfizer submitted a proposed Label Comprehension Study Protocol on February 16, 2017. We have reviewed their proposed Label Comprehension Study Protocol and provided recommendations^a.

Although the proposed renal dose modification table for Lyrica CR is an improvement, we have some concerns with Table 2, 'Lyrica CR Dosage Adjustment Based on Renal Function', within Section 2.5 of the 'Dosing and Administration' section of the proposed PI. (b) (4)

[REDACTED], the row for CLcr greater than or equal to 60 mL/min should read 'No Dosage Adjustment Necessary*', with a footnote indicating the prescriber should refer to dosing recommendation for a specific indication, such as '*Refer to sections 2.1, 2.2, and 2.3 for recommended total daily dose based on indication'. This modification will address the potential for dosing confusion and possible dosing errors in patients with renal impairment.

Sections 2 (b) (4), 'Neuropathic Pain Associated with Diabetic Peripheral Neuropathy', (b) (4)

[REDACTED], the dosing information should outline the recommended starting dose within the first sentence, followed by titration information, and finally maximum dose recommendations last. We recommend to make these changes to section 2.1 for clarity in dosing information.

[REDACTED] (b) (4)

In section 2 (b) (4), 'Postherpetic Neuralgia', we recommend to add the unit of measure 'mg' after the '165' within the first sentence of this paragraph. All doses that are indicted within the PI should be followed by their corresponding unit of measure to ensure users are clear on what the numbers represent.

^a Shah, M. Label Comprehension Study Protocol Review for Lyrica (Pregabalin) Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg and Lyrica oral solution 20 mg/mL IND 53763. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 31. OSE RCM No.: 2017-362.

(b) (4) Table 1, 'Conversion from (b) (4) LYRICA Capsules to LYRICA CR' within section 2.4, reads "When switching from (b) (4) LYRICA to LYRICA CR, on the day of the switch, (b) (4)

(b) (4) This is important dosing information regarding the timing of dosage form conversions that will allow a safe transition from the immediate release formulation to the extended release formulation. This is pertinent information that the user must be aware of prior to converting a patient from an immediate release Lyrica formulation to Lyrica CR. If overlooked, could cause potentially harmful over or under dosing. (b) (4)

Table 1, 'Conversion from (b) (4) LYRICA Capsules to LYRICA CR' within section 2.4, does not address the conversion of Lyrica oral solution to Lyrica CR. For the patients whom require oral solution, there is no guidance on conversion to extended release Lyrica within this table, which may be a source for possible dosing errors. We recommend adding instruction for conversion of the oral solution dosage form to the extended release dosage form to Table 1.

(b) (4)

We noted that Table 2 includes the following symbols: < and ≥. According to the ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations^b, these symbols may be confused or misinterpreted and should be replaced with their full meaning as this may be a source of potential dosing errors. We recommend to replace both symbols, < and ≥ within the proposed PI with their full meaning.

In section 16 of the PI, within the table entitled 'LYRICA CR Tablets' the column outlining tablet strength does not have the unit of measurement, 'mg', following the numerical strength. All strengths that are indicted within the PI should be followed by their corresponding unit of measure to ensure users are clear on what the numbers represent We recommend to add the unit of measure, 'mg' after each numerical strength within the 'Tablet strength' row of this table.

^b ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed Prescribing Information and Medication Guide that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

We find the proposed container labels for Lyrica CR acceptable from a medication error perspective. We have also reviewed the professional sample container label and carton labeling for the 165mg strength and have found both to be acceptable from a medication error perspective.

If you have questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS TO THE DIVISION

We recommend the following be implemented prior to approval of this NDA:

Prescribing Information

- A. In Table 2, within Section 2.5, for patients with normal renal function, (CL_{cr} greater than or equal to 60 mL/min), replace the specific doses with 'No Dosage Adjustment Necessary*', with a footnote indicating the prescriber should refer to dosing recommendations for a specific indication, such as '*Refer to sections 2.1, 2.2, and 2.3 for recommended total daily dose based on indication'.
- B.  (b) (4)
- C. In section 2.1,  (b) (4) the dosing information to follow the recommended starting dose within the first sentence, followed by titration information, and finally maximum dose recommendations last.
- D. In section 2.2, 'Postherpetic Neuralgia', add the unit of measure 'mg' after the '165' within the first sentence of this section.
- E. The sentence within Section 2.4 that reads "When switching from  (b) (4) LYRICA to LYRICA CR, on the day of the switch,  (b) (4)  should be moved to be directly above Table 1, 'Conversion from  (b) (4) LYRICA Capsules to LYRICA CR'.

- F. Add language to Table 1, 'Conversion from [REDACTED] ^{(b) (4)} LYRICA Capsules to LYRICA CR' that will inform user of the appropriate dose conversion of the oral solution dosage form to the extended release dosage form.
- G. In Section 2.4, delete the sentence, [REDACTED] ^{(b) (4)}. This information is contained in Section 3 and is redundant in Section 2.4.
- H. Replace the abbreviation 'd' within Table 1, 'Conversion from [REDACTED] ^{(b) (4)} LYRICA Capsules to LYRICA CR' with the word 'daily'.
- I. Replace the symbols $<$ and \geq , within Table 2, with their full meaning.
- J. In section 16 of the PI, within the table entitled 'LYRICA CR is supplied in the following strengths and package configurations', add the unit of measure, 'mg' after each numerical strength within the 'Tablet strength' row of this table.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lyrica CR (pregabalin) extended release tablets that Pfizer, Inc. submitted on December 15, 2016.

Table 2. Relevant Product Information for Lyrica CR (pregabalin) extended release tablets										
Initial Approval Date	December 30, 2004									
Active Ingredient	Pregabalin									
Indication	Indicated for the treatment of: <ul style="list-style-type: none"> - Neuropathic pain associated with diabetic peripheral neuropathy (DPN) - Postherpetic neuralgia (PHN) - Fibromyalgia 									
Route of Administration	Oral									
Dosage Form	Extended- Release Tablet									
Strength	82.5 mg, 165 mg, 330 mg									
Dose and Frequency	<p>For all indications, begin dosing of LYRICA CR at 165 mg/day. Dosing recommendations for LYRICA CR:</p> <table border="1"> <thead> <tr> <th>Indication</th> <th>Dosing Regimen</th> <th>Maximum Dose</th> </tr> </thead> <tbody> <tr> <td>DPN Pain (2.1)</td> <td>Single dose per day</td> <td>330 mg/day within 1 week.</td> </tr> <tr> <td>PHN (2.2)</td> <td>Single dose per day</td> <td>330 mg/day within 1 week. Maximum dose of 660 mg/day.</td> </tr> </tbody> </table> <p style="text-align: right;">(b) (4)</p> <p>Dose should be adjusted in patients with reduced renal function.</p>	Indication	Dosing Regimen	Maximum Dose	DPN Pain (2.1)	Single dose per day	330 mg/day within 1 week.	PHN (2.2)	Single dose per day	330 mg/day within 1 week. Maximum dose of 660 mg/day.
Indication	Dosing Regimen	Maximum Dose								
DPN Pain (2.1)	Single dose per day	330 mg/day within 1 week.								
PHN (2.2)	Single dose per day	330 mg/day within 1 week. Maximum dose of 660 mg/day.								
How Supplied	Bottles of 30 tablets for each strength									
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).									

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 9, 2017, we searched the L:drive and AIMS using the terms, ‘Lyrica’ and ‘Pregabalin’ to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four (4) previous reviews^{cdef}. We have confirmed that all previous recommendations were considered, with the exception of one review that is currently being evaluated by a DMEPA Safety Evaluator through a Label Comprehension Study Protocol Review, IND 53763, RCM # 2017-362^f. In this review, recommendations have been made to the ‘Pregabalin Dosage Adjustment Based on Renal Function’ table within Section 2 of the currently approved PI. This renal dosing table caused a significant dosing related errors in a patient with renal impairment, and has been the source of confusion for other users as well. These recommendations have been relayed to the Applicant.

^c Toombs, L. Label and Labeling Review for Lyrica (Pregabalin) Oral Solution 20 mg/mL NDA 022488. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 NOV 23. OSE RCM No.: 2009-1083.

^d Kapoor, R. Label, Labeling and Packaging Review for Lyrica (Pregabalin) Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg NDA 21446/S-029. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 NOV 5. OSE RCM No.: 2013-1615.

^e Harris, J. Postmarketing Medication Error Memo for Lyrica (Pregabalin) Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg and Lyrica oral solution 20 mg/mL (NDA 21446 and NDA 22488). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 24. OSE RCM No.: 2011-4313.

^f Shah, M. Label Comprehension Study Protocol Review for Lyrica (Pregabalin) Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg and Lyrica oral solution 20 mg/mL IND 53763. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 31. . OSE RCM No.: 2017-362.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 10, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Nursing and Community Newsletters
Search Strategy and Terms	Match Exact Word or Phrase: Lyrica and Pregabalin

D.2 Results

Our results showed one case discussing a medication dosing error for a patient requiring renal dosage adjustment^g. The error was due to confusion with the renal dosing guideline within the Lyrica PI. This issue is currently being addressed by Pfizer (see OSE Review RCM # 2017-362)^h.

^g Institute for Safe Medication Practices. Safety briefs: Lyrica Dosing Confusion. ISMP Med Saf Alert Community/Ambulatory Care. 2012;5(5):3-4.

^h Shah, M. Label Comprehension Study Protocol Review for Lyrica (Pregabalin) Capsules 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg and Lyrica oral solution 20 mg/mL IND 53763. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 31. OSE RCM No.: 2017-362.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis¹, along with postmarket medication error data, we reviewed the following Lyrica CR (pregabalin) extended release tablets labels and labeling submitted by Pfizer on December 20, 2016.

- Container label
- Professional Sample Carton Labeling
- Professional Sample Container Label
- Prescribing Information
- Medication Guide

G.2 Label and Labeling Images

Container label for 82.5 mg strength:



(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NASIM N ROOSTA
06/23/2017

JAMES H SCHLICK on behalf of OTTO L TOWNSEND
06/23/2017